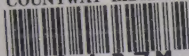


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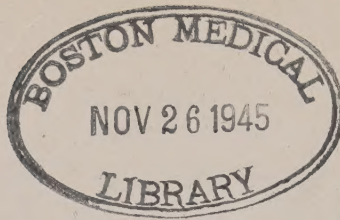
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BREADTHS OF EPIDERMAL RIDGES ON THE HUMAN SOLE

WITH A SUPPLEMENT ON MIDDLE AND PROXIMAL PHALANGES OF FINGERS

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TWO FIGURES

This study was planned with two main objectives: to compare ridge breadths of the plantar and palmar surfaces of the same individuals, and to determine whether the sole presents a systematic topography of variation comparable to that previously demonstrated in the palm (Cummins et al., '41; Ohler and Cummins, '42). All citations herein of specific values for the palm are from the latter publication.

But little investigation of ridge breadth has been accomplished to date. No mass data on ridge breadth of the plantar surfaces have been available. Although Ploetz-Radmann ('37) reports on the ridge counts of middle and proximal phalanges of sixty fingers, it proved desirable to determine such values in members of the present series. All the original literature on the subject of ridge breadth is represented by the papers mentioned above and the few publications cited therein, excepting some new data for non-human primates supplied by Midlo and Cummins ('42).

MATERIAL AND METHODS

The prints here analyzed are from the same subjects earlier used for the examination of ridge breadth on distal phalanges and palms. The subjects are young women (mean age, $18.0 \pm .12$ years; range, 16 to 28 years), all college students. Two of the 100 individuals in the series could not be included in the study of the sole on account of technical faults of the prints, hence the statistics are based upon 98 persons, 196 soles. As explained later, middle and proximal phalanges were analyzed in only 50 of these individuals.

The prints were made by the ordinary printers' ink method, effort being made to secure plantar impressions which are complete as well as cleanly registered. Toes were not printed, hence the analysis must be confined to the sole proper.

For the study of correlation between foot length and ridge breadth, the greatest length of the foot print was substituted for actual foot

length, since foot measurements were not available. These lengths range from (class centers) 19.7 cm. to 24.2 cm., with a mean of 22.2 cm.

Ridge counts were made by the method described by Cummins et al., ridge breadth being indirectly indicated in the number of ridges crossed at right angles by a 1-cm. line. All values presented here are these counts. For each subject counts were made in each of six areas on both soles. The areas selected are the following morphological territories (See Cummins and Midlo, chapter 6): hallucal, interdigital II, interdigital III, interdigital IV, distal hypothenar, calcar. As in previous studies, the value determined for each area is the average of three counts. Calloused regions, showing thickening and spreading of ridges, were avoided.

OBSERVATIONS

Middle and proximal phalanges of fingers

When the counts of ridges on middle and proximal phalanges were being made it was soon discovered that the results would not be as reliable as the counts obtained in other regions. The commonly ill-defined character of ridges over the middle and proximal phalangeal areas proved to be an obstacle to precise counting. Furthermore, it had not been anticipated that the prints would be used for this purpose, and the available impressions of these phalanges are in many instances technically faulty. So few prints carried good registration of the proximal phalanx of the thumb that it was decided to omit consideration of this digit.

In view of the difficulties in counting and assumed consequent inaccuracies, the series was limited to fifty subjects. These were arbitrarily selected in the order of their accession numbers, subjects whose prints were too imperfect being discarded. To avoid a false appearance of precision in the results, the data have not been subjected to statistical analyses such as have been applied elsewhere in the regions admitting more dependable counts. In presenting the individual items mention will be made of our notion of the significance of the values obtained.

Average ridge breadth. The mean count for all middle and proximal phalanges is 18.9 ridges per centimeter. This value is based upon 800 phalanges, 16 in each of 50 subjects. It probably justifies acceptance as a count significantly higher than the lowest value for any other area (17.9, calcar region of the sole) as well as being significantly lower than the regional value next in rank (19.8, palmar thenar/first interdigital).

Regional and bilateral variation. Middle phalanges of the 400 digits have a mean ridge count of 18.8, and the value for proximal phalanges

is 19.0. This slight difference, suggesting a trend toward narrower ridges in proximal phalanges, is reflected also by a tally of the average counts in the two sets of phalanges in individuals: equal counts (considering the counts equal unless they differ by at least one full ridge), 36; the larger count in proximal phalanges, 12; the larger count in middle phalanges, 2. The data are inadequate to demonstrate a real significance, although it is suggestive that a like trend is evident in Ploetz-Radmann's data (her table 7).

Mean counts for individual digits, combining values for right and left and for middle and proximal phalanges, are as follows: II, 18.7; III, 18.6; IV, 18.8; V, 19.7. That digit V has significantly finer ridges than any other seems to be indicated, but whether the three remaining digits are significantly different among themselves remains questionable. Even if not all values are reliable it is interesting to draw comparisons with the findings in apical phalanges, where it has been definitely shown that the digital order of ridge counts is: $IV > V > III > II$. In middle and proximal phalanges the maximum count is in digit V instead of IV. The digital order of ridge counts is $V > IV > II? > III?$. This sequence is repeated in Ploetz-Radmann's material (her table 8).

There is no indication of a bilateral difference of ridge breadth; the means of the combined values for middle and proximal phalanges of right and left hands are identical, 18.9.

Sole

Average ridge breadth. For purposes of comparison the average breadth of plantar ridges of the individual is considered as the mean of the twelve regional counts (six on each sole), without regard to the unlike expanses of the several regions. The mean is 22.0 ridges per centimeter, to be compared with a mean of 21.1 ridges in the palms of the same subjects; the difference is statistically significant (table 1). By this analysis, therefore, the sole is shown to possess finer ridges than the palm.

The finding is rather unexpected in the light of the impression gained from mere inspection of prints that plantar ridges are the coarser. The impression undoubtedly arises from the fact that the posterior area of the sole, characterized by ridges much coarser than those in any palmar region, is extensive and conspicuous. Tallies of comparative counts in palm and sole (table 2) demonstrate the pronounced differential of corresponding regions in the two members, supplementing the evidence of unlikenesses revealed in the mean values (fig. 2).

TABLE 1

Counts of ridges per centimeter compared in palms and soles of the same subjects (hands, 100 individuals; soles 98): Frequency distributions of the counts in single hands (values for all palmar areas combined) and in single feet (all plantar areas combined).

RIDGES PER CENTIMETER, CLASS CENTER	FREQUENCY	
	Palm	Sole
17.7	1.0%	...%
18.2	1.5	...
18.7	4.5	...
19.2	9.0	1.0
19.7	9.5	3.1
20.2	13.0	4.1
20.7	16.5	8.2
21.2	10.0	13.8
21.7	8.0	22.5
22.2	8.0	13.8
22.7	4.0	10.2
23.2	4.0	10.2
23.7	2.0	8.7
24.2	3.0	2.6
24.7	3.5	1.5
25.2	2.0	0.5
25.7	0.5	...
Mean and P.E.	21.1 $\pm$ 0.08	22.0 $\pm$ 0.06
Standard deviation and P.E.	1.7 $\pm$ 0.06	1.2 $\pm$ 0.04

TABLE 2

Ridge counts (per centimeter) compared in soles and palms of the same individuals (98): frequencies of the individuals who present the indicated relationships between values for palms and soles. The values compared are averages of right and left sides. Average counts differing only by a fractional ridge are rated as equal.

	PLANTAR AND PALMAR COUNTS EQUAL	PLANTAR COUNT GREATER THAN PALMAR	PLANTAR COUNT LESS THAN PALMAR
Calcar and proximal palm (hypothenar and thenar)	12.2%	...%	87.8%
All areas ¹	49.0	40.8	10.2
Distal regions only ²	34.7	60.2	5.1

¹ Sole: hallucal, interdigitals II-IV, distal hypothenar and calcar. Palm: hypothenar, thenar and interdigitals II-IV.

² Sole: hallucal and interdigitals II-IV. Palm: interdigitals II-IV.

If it were possible to establish topographic limits for separate areas it would be desirable to establish "weighted averages" for the sole and for the palm, the ridge count for each area being weighted in accord with the expanse of that area. From one point of view it is obviously a discrimination to attach as much weight to a small area, perhaps an area with very fine ridges, as to a large one in which the ridges are coarse. But in view of the technical difficulties attending adjustment of average values in this manner, it seems better to forego the attempt than to create an appearance of exactness in a procedure that does not lend itself to precise quantitative methods. Still, a comparison may be drawn between palm and sole on a rough basis, to indicate the direction of results that would be obtained. The proximal portion of the palm (hypothenar and thenar/first interdigital zones), which bears coarse ridges, is about twice the area of the distal region (interdigitals II-IV), and if the ridge-count values for these two collective regions are correspondingly weighted the average for the palm is reduced to 20.9 (from 21.1, table 1). Then, assuming that the entire proximal region of the sole, about equal in expanse to the distal area, bears ridges corresponding in breadth to those measured in the calcar region, the weighted average for the sole as a whole is lowered to 20.4 (from 22.0, table 1). This comparative device enables us to understand the impression gained from casual inspection of sole prints, that the sole possesses coarser ridges than the palm; yet for general purposes it is expedient to compute the average ridge count from determinations in the several morphological territories as we have done.

Regional variation. Table 3 lists the mean ridge counts for the six plantar areas; figure 1 is designed for ready inspection of the topographic trends of variation in ridge breadth and for comparison of the corresponding trends in the palm. For comparison of ridge counts in individual areas, the values for right and left soles are combined in an average (table 3).

The calcar region, with a count of 17.9, exhibits the coarsest ridges of the sole, and indeed of any area. Its distinctiveness is real, as indicated by the following significance ratios in comparison with other areas: hallucal, 31; interdigitals II, III and IV respectively, 56, 71 and 75; hypothenar, 28. The order of progressively increasing ridge counts in the several areas is: distal hypothenar and hallucal, 20.7; interdigital II, 23.5; interdigital IV, 23.8; interdigital III, 25.6. There is no difference between the distal hypothenar and hallucal areas, and the difference between interdigital areas II and IV is insignificant. However, the hallucal and distal hypothenar regions differ significantly from

TABLE 3

Mean ridge counts per centimeter in individual plantar areas (98 persons, 196 soles), with standard deviations and coefficients of variation.

	MEAN AND P.E.			STANDARD DEVIATION AND P.E.			COEFFICIENT OF VARIATION AND P.E.		
	R	L	R + L	R	L	R + L	R	L	R + L
Hallucal	20.6 ± .11	20.8 ± .11	20.7 ± .08	1.54 ± .07	1.61 ± .08	1.58 ± .05	7.5 ± .36	7.7 ± .38	7.6 ± .26
Interdigital II	23.5 ± .12	23.5 ± .11	23.5 ± .08	1.69 ± .08	1.65 ± .08	1.67 ± .06	7.2 ± .35	7.0 ± .34	7.1 ± .24
Interdigital III	25.7 ± .13	25.6 ± .13	25.6 ± .09	1.88 ± .09	1.89 ± .09	1.87 ± .06	7.3 ± .36	7.4 ± .36	7.3 ± .25
Interdigital IV	23.9 ± .13	23.7 ± .13	23.8 ± .09	1.84 ± .09	1.96 ± .09	1.91 ± .06	7.7 ± .38	8.3 ± .40	8.0 ± .28
Distal hypothenar	20.7 ± .11	20.7 ± .11	20.7 ± .08	1.66 ± .08	1.63 ± .08	1.64 ± .06	8.0 ± .39	7.9 ± .38	7.9 ± .27
Calcar	17.9 ± .09	17.9 ± .09	17.9 ± .06	1.27 ± .06	1.34 ± .06	1.31 ± .04	7.1 ± .35	7.5 ± .36	7.3 ± .25
Entire distal sole ¹	23.4 ± .09	23.4 ± .09	23.4 ± .07	1.34 ± .06	1.37 ± .07	1.36 ± .05	5.7 ± .28	5.9 ± .28	5.8 ± .20

¹ This is a combination value for all areas except the distal hypothenar and calcar.

each of the three interdigital areas (the respective significance ratios being 26, 43 and 27). The significance ratio of the difference between interdigitals II and III is 18, and that of interdigitals III and IV, 14.

Considering first the distal row of patterns (sole: hallucal, interdigitals II-IV; palm: interdigitals II-IV, it will be noted that in sole as in palm the site of minimum ridge breadth (i.e., the largest count per centimeter) is interdigital III. On either side of this area, ridge breadth increases (i.e., the counts decrease). Ridge breadth increases still more in the more proximally situated dermatoglyphic zones (sole:

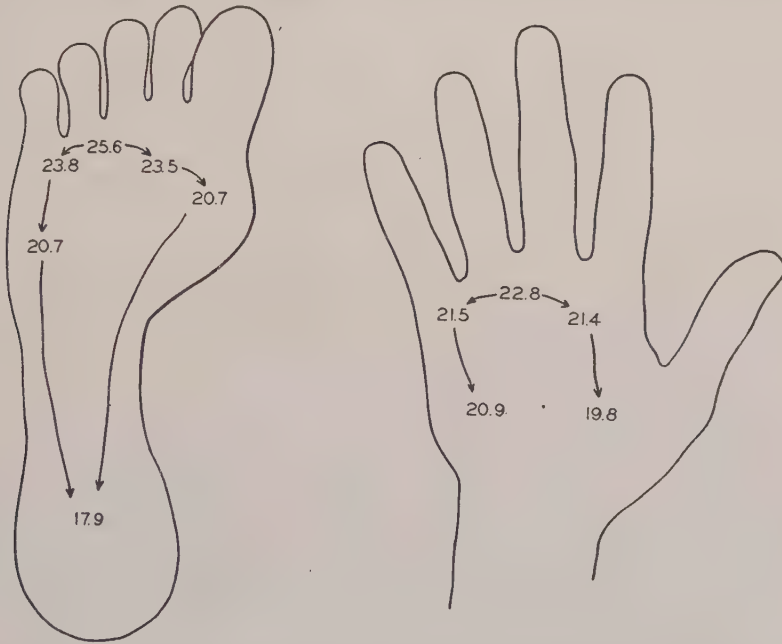


Fig. 1 Regional variations in ridge breadth of the sole and palm (the latter from Ohler and Cummins). The figures, inserted in the individual territories where counts were made, represent average counts of the ridges transversely crossing a 1-cm. line; these values obviously bear an inverse relation to ridge breadth.

distal hypothenar, calcar; palm: hypothenar, thenar). The palmar areas selected for counting admit comparison of only two transverse levels, but in the fibular portion of the sole there are three levels (in order: interdigital IV, distal hypothenar, calcar) with counts indicating that ridge breadth increases progressively in a disto-proximal direction. This gradient of increasing ridge breadth has been emphasized in the two previous studies of hands, where it is shown that the increase progresses from apical phalanges to the palm, and from the distal palm into the proximal palm. With the new information regarding ridge breadth

over the phalanges it is now clear that the relation of gradients is not as simple as it first appeared; these regions introduce a sharp break in the sequence.

The data illustrated in figure 2 are adapted for ready inspection of this broken disto-proximal gradient. The values inserted in the outlines of hand and foot are average values for right and left members, and when the levels are represented by more than one dermatoglyphic territory they are averages of values for the two or more territories involved. Thus in the hand 25.4 is the average count for all five apical

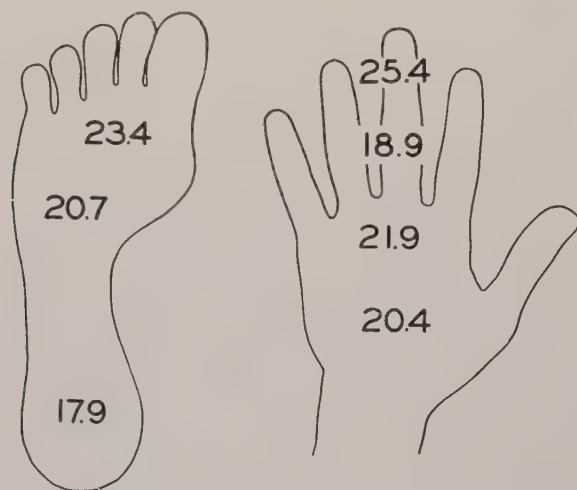


Fig. 2 Condensation of ridge-count values, adapted for ready inspection of trends of disto-proximal variation. Values for the hand, excepting that of middle and proximal phalanges, are from Ohler and Cummins. The figures, as before, are averages of ridge counts per cm., but in this illustration some are collective values for two or more individual areas as here listed. Sole: 23.4 = "distal sole," the average of hallucal and interdigitals II-IV; 20.7 = distal hypothenar; 17.9 = calcar. Palm: 25.4 = average of the five apical phalanges; 18.9 = average of the distal and proximal phalanges, digits II-V; 21.9 = "distal palm," the average of interdigitals II-IV; 20.4 = "proximal palm," the average of hypothenar and thenar/interdigital I.

phalanges, 18.9 represents the middle and proximal phalanges of digits II-V, 21.9 is the average of interdigitals II-IV, and 20.4 is the average of hypothenar and thenar counts. In the foot 23.4 is the average of four territories, the hallucal area and interdigitals II-IV, while the counts 20.7 and 17.9 represent single regions, the distal hypothenar and calcar respectively.

Comparison of right and left soles. Three of the six plantar areas yield identical mean counts in right and left soles, and the remaining three have counts which are insignificantly different on the two sides.

The lack of bilateral difference is in contrast to the previously demonstrated trend of apical phalanges of fingers toward coarser ridges in right hands, but is not unexpected in view of the finding of negligible bilateral differences in palms.

The relation of ridge breadth and foot length. A small degree of inverse correlation between foot length (measured on the prints as described above) and average ridge count is indicated by the coefficient $-.22 \pm .07$, a value which agrees closely with the coefficients of correlation for hand lengths and ridge counts reported in the independent series of males and females.

Variability. The coefficients of variation for individual areas (table 3) range from 7.1 to 8.0, which compares closely with the values obtained in the palmar areas (7.1 to 8.8). It is apparent, therefore, that the magnitude of variation in the sole is on a par with that in the palm.

DISCUSSION

The intermembral differences of ridge breadth and the regional variations within the hand and foot offer an interesting subject for speculation. In the present state of knowledge any explanation of these variations which is advanced must be only tentative, the need for guarded interpretations being well illustrated by the modified views which have issued from the present study.

When the two investigations of hands were reported, emphasis was placed upon the disto-proximal gradient of increasing ridge breadth. The apical phalanges collectively were found to present the narrowest ridges of the hand; ridge breadth was greater in the distal palm and still greater in the proximal region. The same sequence is here indicated in the sole. However, it is now evident that some factor or factors other than a simple relationship in the longitudinal axis must be concerned, because a distinct break in the distoproximal gradient is introduced by the very coarse ridges of the middle and proximal phalanges of fingers. The explanation of both this aberrancy and adherence of the palm and sole to the gradient probably is to be sought in differential growth, as discussed below.

Another principle which was stressed in the previous studies of hands is a gradient of increasing ridge breadth from loci having a proximate relation to the anatomical axis. On the palm the narrowest ridges occur in the region of interdigital III; ridge breadth increases on either side of this area. Among finger tips the narrowest ridges are on digit IV; ridge breadth is greater on digit V, and in the digital series the increase of breadth is progressive from IV to I. New data furnished by

the present study discount the importance of relationship to the anatomical axis. First, the narrowest ridges of middle and proximal phalanges are not localized on finger III or IV, where they would be expected if the anatomical axis exerts an independent control, but occur instead on finger V. Second, the narrowest ridges of the soles are not localized in interdigital II, to coincide with the anatomical axis; they are found in interdigital III, a site homologous to the region of narrowest ridges in the palm. These irregularities indicate that the anatomical axis, as such, can hardly be regarded as a source of influences regulating ridge breadth, unless such control as it may exert is masked or distorted by other factors which are secondarily introduced.

There are suggestive indications that sustained friction may coarsen ridges (see Cummins et al.). Even if such an effect be conceded there is little likelihood that differential use alone can account for the wide differences in ridge breadth demonstrated among the areas of the one member or between hand and foot. If friction and weight-bearing produced ridge-coarsening it would be difficult to explain away the existence of ridges in the ball region of the sole which are finer than those borne anywhere on the palm. There must be some more deep-seated agency in control of ridge breadth, leading to regional unlikenesses which are so extreme that they are not nullified by the possibly superimposed factor of use.

It is possible that genetic factors in control of ridge breadth play a rôle in producing individual and regional differences, although we are inclined to search for a more immediate explanation. Only a hint of this explanation, on the basis of differential growth, has been offered before (Cummins et al.). Further consideration, especially in the light of the collected findings in both members, convinces us that differential growth should receive serious attention as a possible major element in the regulation of ridge breadth.

Direct evidence supporting the idea which is here briefly introduced is obtainable by examination of ridge breadth in fetuses of graded ages, and such determinations will be made as a part of a larger project concerned with the embryology of dermatoglyphics which is about to be undertaken in this laboratory (by Mrs. Eleanor S. Gould). In the meantime, it will be of interest to mention certain facts which are suggestive of the influence of differential growth.

It will be recalled (Cummins and Midlo, chapter 10) that the critical stages of ridge differentiation occur in the third and fourth fetal months. Ridges are not formed simultaneously over the whole hand or foot. In the hand they appear first on apical phalanges, then in areas

of the palm and finally on middle and proximal phalanges. Ridge differentiation in the foot is tardy, as compared to the hand; preliminary observations indicate that the spread of originally isolated sites of ridge formation in general conforms to that of the hand.

Ridge formation is completed at a time when the form and proportions of the hand and foot are still quite unlike the state of the adult. An excellent illustration of these dimensional changes is furnished in a figure published by Schultz ('26, fig. 9). This figure represents a hand and foot each of a fetus of the ninth week, a newborn infant and an adult — drawn to uniform lengths. To select examples of differential growth, attention may be directed first to the changed proportions of finger segments. In the fetus, compared with the newborn and especially the adult, the apical phalanges are relatively large, while middle and proximal phalanges are small. Thus in attaining adult proportions growth is more accelerated in the middle and proximal phalanges than in apical phalanges. In the palm growth becomes more accelerated in the proximal region, and in the sole likewise — the effects of differential growth being especially marked in the latter, where the relative prolongation is greater. The regions exhibiting increased relative rates of growth, after the period of ridge differentiation, are the very regions which present broader ridges. It seems possible, therefore, that epidermal ridges may be at first more nearly uniform in breadth, and that growth of ridges already formed keeps pace with the unequal growth of different regions. Whether or not this is the case can not be stated until the study just mentioned has been carried out.

SUMMARY

1. Breadths of epidermal ridges, in terms of ridge count per centimeter, were determined in six morphological territories of the sole and in middle and proximal phalanges of fingers. The subjects (soles, 98 persons; phalanges, 50) were young women from the series previously used in a study of ridge breadth of the palm and apical phalanges.

2. The distal region of the sole presents narrower ridges than the homologous territory of the palm. Ridges of the proximal sole are coarser than those in any other region of the sole or hand. Middle and proximal phalanges of fingers bear ridges next in coarseness to the proximal sole.

3. The sole exhibits a topography of regional variations in ridge breadth which corresponds in principle to that of the palm. Ridges are narrowest in the third interdigital area; in regions on either side of this area, and in regions proximal to it, ridges are broader.

4. There is no significant differential of ridge breadth in right and left soles.

5. A weak positive correlation between foot length and ridge breadth exists, comparable to that between hand length and ridge breadth.

6. Variability of ridge breadth of individual areas of the sole is equal in magnitude to that displayed in the palm.

7. Stress is accorded the possibility that differential growth may be a major factor responsible for intermembral distinctions of ridge breadth and for regional differences within the one member.

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ABSENCE OF THE OPTIC NERVE IN CYCLOPIA

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FIVE FIGURES

The study of cyclopia and related median defects of the head has contributed much to general teratology as well as to our knowledge of the developmental mechanics of the eye. A wealth of pertinent information has been gathered by Adelmann ('36) in a review which will be referred to in the following pages instead of extensive quotations from individual reports. There is general agreement that the median and symmetrical defects found in cyclopia as well as in lesser degrees of the malformation, such as synophthalmia, are not the result of elimination of tissue, although similar defects have been produced experimentally by the destruction of a median area of the embryonic head (Wolff, '34). Since the most striking abnormalities in cyclopia are found in derivatives of the neural plate, the efforts of early investigators were directed toward the exact localization of the prospective defect in the neural plate stage. Diagrams outlining the position of the prospective parts of the eye in the neural plate have been prepared by Fischel, and the defects found in various degrees of cyclopia traced on these maps. These diagrams have been improved and modified by various subsequent investigators (see the review of Adelmann). In spite of minor differences most authors agreed that the parts missing in cyclopia are located in a wedge-shaped median area of the neural plate which could be demonstrated in these diagrams. Various degrees of the malformation could thus easily be explained by a varying width or angle of the wedge. No information could be obtained by these speculative methods on the mechanism of the developmental anomaly.

A new trend in the study of cyclopia appears in the work of Adelmann ('30) and Mangold ('31) who showed that an abnormality in the determination of the parts in an originally normal neural plate, without an actual defect in it, produces cyclopia. This was accomplished by experimental elimination of parts of the underlying mesoderm. It thus appears that the less conspicuous defects of mesodermal parts of the head may be of greater importance in the primary mechanism of cyclo-

pia formation than the obvious abnormalities of the eyes and brain. Adelmamm's own work and other data compiled in his review have since made it abundantly clear that this point of view, stressing abnormal determination of the parts rather than the absence of their tissue, deserves full recognition. A similar view was recently advanced regarding the common form of sporadic microphthalmia in the chick (Gruenwald, '44). This concept obviously reduces the importance of the maps of eye-forming areas designed by earlier authors. Furthermore, we now know that the parts of the eye primordium are determined in a very labile manner, if at all, in the neural plate stage (Hoadley, '36; Mangold, '31, Gruenwald, '44). The question is no longer one of defining the extent of an early embryonic defect in the neural plate, but rather one of investigating the agents acting upon a primarily normal neural plate, and influencing its determination. However, diagrams showing the presumptive cyclopic defect in the neural plate are still helpful in recording the defects, and thus the effects of normal and abnormal determining agents. In these considerations defects of the optic nerve play a considerable role, and this particular aspect of the cyclopia problem will be dealt with in the present report.

Absence of the optic nerve is a common occurrence in otherwise well developed cyclopic eyes. In order to account for this, Fischel showed in his diagrams how the region of the prospective optic stalk, which he placed in the neural plate in a position medial to the eye itself, is comprised entirely in the wedge-shaped defect of cyclopia. Consequently, he assumed that these cyclopic eyes develop without optic stalks, and therefore constrict themselves off completely from the brain. However, Petersen soon showed that the area of the optic stalk surrounds the entire eye-forming region in the neural plate, as retina and tapetum are separated everywhere from the brain wall by the optic stalk. A similar corrected diagram was subsequently devised by Woerdeman. Figure 1, which corresponds in its essential features with the diagrams of Petersen and Woerdeman, shows that no median defect leaving any trace of the eye-forming areas, can eliminate the entire stalk region. Assuming for the purpose of discussion that considerations based on these maps of presumptive areas have any value, one can see that any median eye formed from the remaining areas after elimination of a median and symmetrical region, must have an optic stalk (fig. 1b).

A recent study of microphthalmia in chick embryos has revealed facts about the development of the optic nerve which, when applied to cyclopic eyes, make it probable that the latter actually develop from

a primordium corresponding to the postulate illustrated by figure 1b, that is, from an optic cup with an optic stalk. It will presently be shown that this hypothesis is borne out by the examination of cyclopic embryos.

Among the previously studied microphthalmic chick embryos, all specimens from the first 6 days of incubation show optic stalks, regardless of the type and degree of microphthalmia. In normal, and part of the maldeveloped eyes nerve fibers begin to grow from the retina into the stalk during the fifth day. No such growth occurs in certain malformations, and in these cases characteristic changes appear in the optic stalk during the seventh day. The stalk rapidly becomes thinner, and is soon interrupted. In later stages, only those optic stalks are found which have been penetrated by nerve fibers from the retina. No nerveless stalks were seen in any of the malformed embryos of the

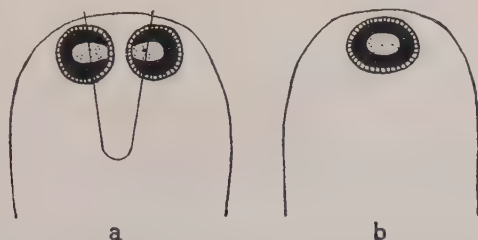


Fig. 1 Diagram of the approximate location of the eye-forming areas in the neural plate. a, normal condition; b, cyclopia, assuming a defect as outlined in a. Retina: stippled; tapedum: black; optic stalk: cross lined.

second or third week except for occasional small, pigmented remnants attached to the eye. It thus appears that absence of an optic nerve and complete separation of the eye from the brain is a secondary condition, brought about by degeneration of the optic stalk if no nerve fibers penetrate it at the proper time.

There are two conditions in microphthalmic eyes, in which no fibers grow into the optic stalk. One of these is absence of the retina, and the other absence of the chorioid fissure, even in otherwise perfect eyes. The present figure 3, taken from the previous series of observations, is from an embryo of the seventh day with severe microphthalmia and absence of the retina on the left side, and absence of the chorioid fissure in the otherwise normal right eye. The changes in both optic stalks are essentially alike, and consist of thinning and interruption at about equal distances from the brain and eye. Figure 3 is taken from the right side.

If one studies the diagrams of figure 1 with these facts in mind, it is apparent why many cyclopic eyes have no optic nerve. In the nor-

mal eye (fig. 1a) the future chorioid fissure appears in the neural plate stage as an area of direct contact of retina and optic stalk material on the medial side of the eye-forming region. If the defect is sufficiently extensive, a cyclopic eye is formed in which this contact of retina and stalk does not exist (fig. 1b), in other words, an eye without a chorioid fissure. The optic stalk will then degenerate secondarily. This explains the absence of the optic nerve in cyclopia more satisfactorily than the hypothetical constricting-off of an eye primarily devoid of an optic stalk. Primary absence of the stalk results in a different appearance, as was illustrated by another microphthalmic embryo preserved on the ninth day of incubation when no further fundamental changes can be

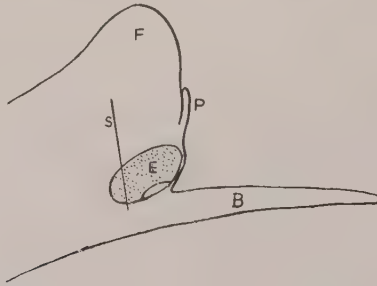


Fig. 2 Sketch of a lateral view of the head of the cyclopic chick embryo L 38. B, lower beak; E, single median eye; F, bulge caused by the undivided forebrain; P, proboscis; S, line indicating the approximate level of the section shown in figure 4.

expected. The pigment epithelium of the left eye is directly attached to the brain wall along a line roughly corresponding to the equator of the eye, and the retina bulges into the ventricle ('44, fig. 23). The eye did not constrict itself off from the brain as was suggested by Fischel. In fact, one of Fischel's own specimens, a salamander larva shown in his figures 40 and 41, shows the tapetum directly attached to the brain wall.

The following observations in cyclopic specimens will confirm the suggestion that the optic nerve is absent in these cases in which no chorioid fissure had developed.

OBSERVATIONS

Only in certain cases of cyclopia without an optic nerve is it possible to verify the hypothesis than an optic stalk, but no chorioid fissure had existed in early stages. In mammals and man, no trace of the chorioid fissure remains after its closure in the normal eye. In certain other vertebrates, however, characteristic permanent structures remain in

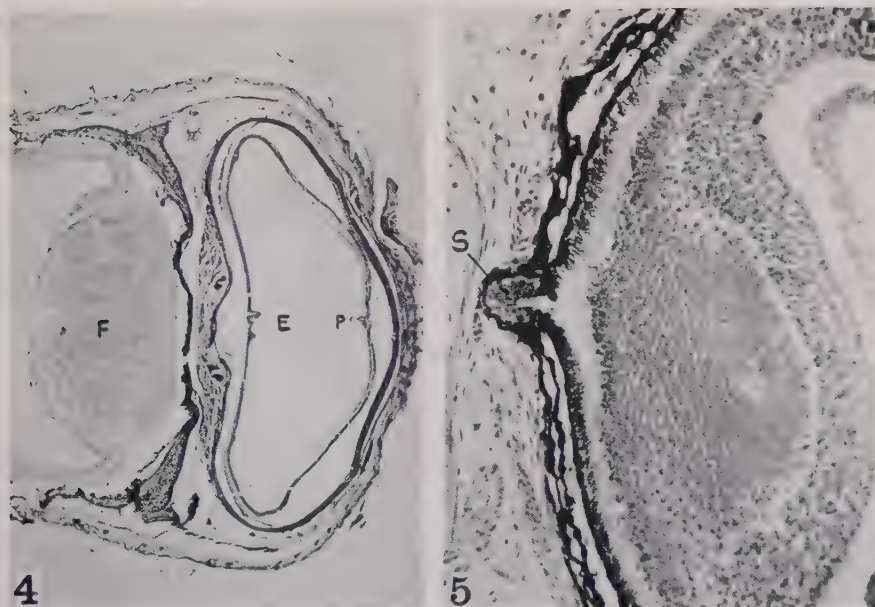
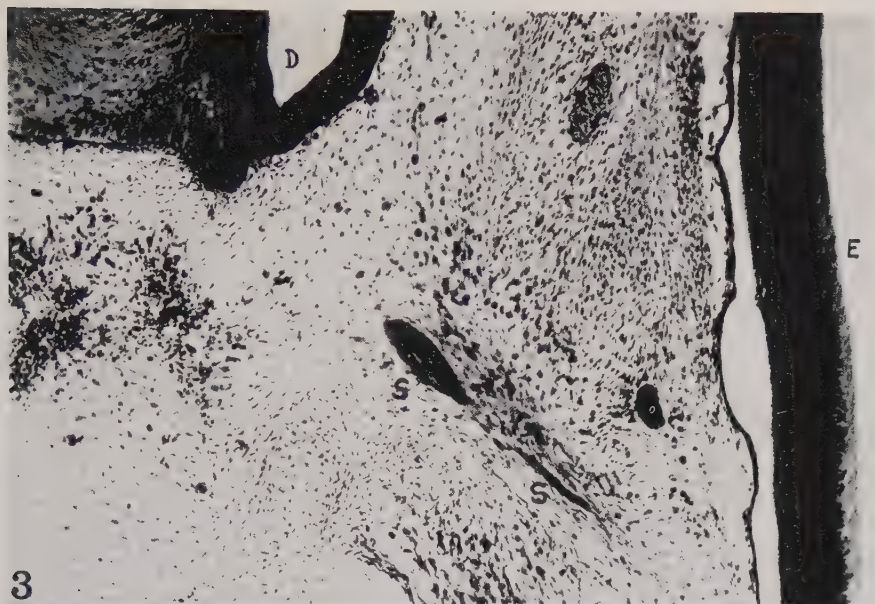


Fig. 3 Microphthalmic chick embryo E 745 (see Gruenwald, '44). D, diencephalon; E, eye with absence of chorioid fissure; S, optic stalk. Serial sections show that the proximal portion of the stalk connects with the diencephalon, and the distal one with the pigment epithelium. However, the two portions are not connected with each other.

Fig. 4 Cyclopic chick embryo L 38, section at the level indicated in figure 2, S. E., eye; F, forebrain; P, pecten-like rudiment (see text).

Fig. 5 Cyclopic larva of *Salamandra maculosa*. A short, pigmented remnant of the optic stalk (S) is attached to the pigment epithelium, but not to the retina. It contains no nerve fibers. There is no chorioid fissure.

the place of the chorioid fissure, such as the pecten in birds. This gives an opportunity to ascertain by examination of late stages, whether or not a chorioid fissure had existed. Efforts to do this have been successful in a chick embryo and a salamander larva.

Among many maldeveloped chickens and embryos generously given by Dr. W. Landauer, one case with a well developed cyclopic eye was found (embryo L 38, from the end of the incubation period). The gross appearance of the head is sketched in figure 2. The upper beak is completely absent while the lower beak is normally developed. The skull is small and has a protrusion which grossly could be seen to contain a single, thin-walled portion of the brain, apparently corresponding to the fused hemispheres. The large, single, median eye faces rostrad and ventrad. Its pupil is directed toward the tongue. A proboscis is present in the typical location above the eye. The head was sectioned serially after removal of the lower beak, and every fifth 12- μ section was mounted and stained by the azan method. Examination of the sections confirmed the identification of the protruding brain vesicle as an undivided forebrain. The eye is also undivided, except for small folds of the retina in the midline above and below the pupil which probably indicate duplicity. Both the optic nerve and the pecten are absent. If a pecten were present, it should be seen in the section shown in figure 4 which is taken from the lower part of the eyeball, as indicated in figure 2. There is a small structure resembling a pecten (fig. 4, P), but this was found in only a few sections of the series, and nowhere larger than in the figure. It is located near the ciliary portion of the retina, far from the region where an optic nerve would develop, and the two layers of the optic cup are not connected with each other at this pecten-like rudiment. It must therefore be assumed that this structure is not a pecten, but perhaps related to the folds which were found in the retina in the midline. It can be concluded that the cyclopic eye of this embryo had no chorioid fissure in its early development, as postulated in the proposed hypothesis.

A more direct indication of absence of the optic nerve being caused by absence of the chorioid fissure was seen in a cyclopic larva of *Salamandra maculosa*. This specimen was received serially sectioned at 10 μ , and stained with hematoxylin and eosin. The forebrain shows no division into hemispheres. The oral end of the fore-gut does not open to the outside. A well developed single, median eye is present. All indications of a chorioid fissure which can clearly be seen in normal eyes of comparable age as an inward folding of the tapetum, are absent. There is no optic nerve. Only a short distal remnant of the optic stalk is

attached to the tapetum (fig. 5). It is purely epithelial, pigmented, and not connected with the retina. It contains no nerve fibers. Perhaps pigmentation, or a peculiar differentiation indicated by it, has prevented degeneration of this small portion of the optic stalk in the absence of nerve fibers, as was also seen at microphthalmic chick embryos ('44). In this instance the original presence of an optic stalk, and failure of nerve fibers to grow into it because of a lack of continuity of retina and stalk, is beyond doubt.

These are the only available cases of cyclopia with well developed eyes in which information on the chorioid fissure could be expected. Absence of the optic nerve in the presence of indications of a chorioid fissure has not been observed.

There is another possibility of recognizing that an optic stalk had existed, and secondarily degenerated. This was also suggested previously ('44) by findings in a microphthalmic chicken in which the nerve was absent due to absence of the retina. A tube-like sheath connected the dura with the sclera, and it was suggested that the stalk had induced differentiation of the sheath before degenerating. This is not the rule in the chick, but it might occur in man and mammals and would, if found in cyclopia, present a confirmation of the present results.

CONCLUSION AND SUMMARY

The present observations in two cyclopic embryos of widely distant groups of vertebrates, in conjunction with previous findings in microphthalmia, indicate that in cyclopia as well as in microphthalmia the absence of the optic nerve is not due to a primary absence of the optic stalk. All eyes with the exception of those directly attached to the brain, have an optic stalk during their early development. If nerve fibers fail to grow through the stalk as it happens in the absence of a chorioid fissure, the stalk soon degenerates. Primary absence of the optic stalk results in permanent attachment of the tapetum to the brain wall and communication of the cleft between retina and tapetum with the ventricular system of the brain.

The present evidence of lack of a chorioid fissure in certain cyclopic eyes, conforms with the pattern which may be obtained by mapping out the prospective parts of the eyes in the neural plate, and assuming a median defect. In the light of recent information concerning the genesis of cyclopia, this should not be evaluated as evidence of a primary absence of tissue in the median portion of the neural plate, but rather as the result of abnormal determination, perhaps because of a defect of the underlying mesoderm.

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THE THYROTROPHIC POTENCY OF THE PITUITARIES OF ALBINO MICE WITH RESPECT TO AGE AND SEX

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ONE FIGURE

The amount of thyrotrophin in the anterior pituitaries of mammals of both sexes at different ages has been determined to some extent for cattle, swine, rats, rabbits, guinea pigs and human beings. The method of assay has usually been the implantation of fresh pars anterior or the injection of a suspension made from frozen or dried glands into a suitable recipient, such as the guinea pig, rabbit, chick, dove, sparrow or canary and the estimation of the response of the recipient's thyroid by the changes in its cells and colloid or by determining the increase of weight or cell height over that of the untreated control. Some investigators have also used these criteria in testing body fluids, such as blood serum or urine, for their content of thyrotrophin.

There has been considerable variation in the results of investigation of the thyrotrophic content of the pituitary or of body fluids as related to both age and sex. In general, they have indicated an increase during periods of rapid growth, followed by a decrease after sexual maturity has been fully established (rat: Turner and Cupps, '39; rabbit: Saxton and Greene, '39;¹ Bergman and Turner, '41; guinea pig: Aron, '31; cattle: Bates, Riddle and Lahr, '35; Reece and Turner, '37; swine: Elijah, '40, cited by Bergman and Turner, '41), although according to a few reports, the change has been slight or absent (human: Aron and Klein, '30; Müller, Eitel and Loeser, '35; Saxton and Loeb, '37; Witschi and Riley, '40). No significant difference in the amount of thyrotrophin in the two sexes has been reported by some investigators (rabbit: Chen and Van Dyke, '36; Saxton and Greene, '39; Bergman and Turner, '41; cattle: Bates, Riddle and Lahr, '35; human: Aron and Klein, '30; Müller, Eitel and Loeser, '35; Witschi and Riley, '40), while by others it has been claimed that the male anterior pituitary is more potent than the female one (rat: Turner and Cupps, '39; cattle: Reece and Turner, '37).

¹ Saxton and Greene ('39) report a greater potency in immature rabbits (10-70 days) than in young mature ones (4-8 months old), but a decrease in old females compared with young mature ones.

The present tests have been undertaken to determine the amount of thyrotrophin in the anterior pituitaries of male and female albino mice of one strain at three ages: prepuberty (26–27 days), puberty (40–41 days) and early sexual maturity (82–83 days). The assay used has been the 24-hour chick test in which an increase of 100% over that of controls in the average thyroid cell height of a group of 1- or 2-day-old chicks 24 hours after subcutaneous implantation of the anterior pituitary is considered to represent the effect of one chick unit of the hormone (Adams and Beeman, '42). Furthermore, the thyroid cell heights of the mice furnishing the anterior pituitaries for testing have been measured in an effort to correlate this indicator of thyroid activity with the amount of thyrotrophin present in the anterior pituitary and thus to attempt an interpretation of the release-storage relationship of the thyrotrophin in the mice at the three periods of life studied.

MATERIALS AND METHODS

The albino mice whose anterior pituitaries and thyroids were used in this study were purchased from Strong's Breeding Laboratory in Woodbridge, Connecticut. Males and females were placed in separate cages in a room where the temperature ranged from 70 to 75°F. and were fed on Pratt's Nurishmix and fresh lettuce. There were three series of animals: I, 7 males and 6 females, 26–27 days old; II, 4 males and 4 females, 40–41 days old; and III, 6 males and 6 females, 82–83 days old. The 2-day-old chicks used in assaying the thyrotrophin of the mouse pars anterior were a cross between the Rhode Island Red male and the Barred Rock female and were purchased from the Pilch Poultry Farm at Hazardville, Connecticut. Each mouse was killed by severing the cord at the base of the brain, its pars anterior was removed, weighed on a precision balance and then implanted subcutaneously in the breast of a 2-day-old chick. Twenty-four hours later, the chick was killed with ether, its thyroids removed, weighed and fixed for sectioning in Helly's fluid. The thyroids of control chicks which were either untreated or implanted with mouse brain 24 hours prior to killing were handled similarly. The thyroids of each mouse were dissected out, weighed and fixed in Helly's fluid as soon as possible after the anterior pituitary had been implanted. Tissues were sectioned at 5 μ and stained in Delafield's hematoxylin followed by Mallory's triple connective tissue stain.

The follicular epithelium of the thyroids of the chicks and the mice was measured at a magnification of 950 times with a Leitz ocular micrometer. The highest and the lowest cell in each of fifty follicles located

in a section near the middle of the chick thyroid (or in two or three sections, five sections apart in the mouse thyroid) were selected for measuring. This is a modification of the method of Rawson and Starr ('38) and Rawson and Salter ('40). Two diameters at right angles to each other were also determined for 25 follicles in each of the mouse thyroids to see if follicular size varied with age and sex. After measurements of the chick thyroids were completed, the chick units of thyrotrophin (Adams and Beeman, '42) per gram of fresh pars anterior were calculated.

OBSERVATIONS

Mouse thyroids (table 1). The thyroids of the 26- to 27-day-old mice were active as judged by the average cell height, that of the female ($5.58 \pm 0.06 \mu$) being significantly higher than that of the male

TABLE 1

Data concerning mice whose anterior pituitaries (AP) were assayed for thyrotrophin (see table 2).

SERIES OF MICE	SEX	NUMBER OF ANIMALS	AVERAGE BODY WT. (GM.)	AVERAGE AP WT. (MG.)	AVERAGE ABSOLUTE THY. WT. (MG.)	AVERAGE THY. CELL HT. (μ)	AVERAGE THY. FOLL. DIA. (μ)
I 26-27 days old	♂	7	13.5	0.42	1.41 ¹	5.11 ± 0.04^1	38.06 ± 0.53^1
	♀	6	10.4	0.33	1.02	5.58 ± 0.06	36.45 ± 0.57
	♂ and ♀	13	11.9	0.38	1.22 ²	5.35 ± 0.03^2	37.02 ± 0.38^2
II 40-41 days old	♂	4	16.6	0.52	1.37	5.79 ± 0.07	40.75 ± 0.80
	♀	4	10.7	0.40	0.70	4.96 ± 0.06	36.45 ± 0.72
	♂ and ♀	8	13.6	0.46	1.03	5.38 ± 0.04	38.60 ± 0.54
III 82-83 days old	♂	6	19.1	0.85	1.94	5.41 ± 0.04	43.03 ± 0.68
	♀	6	19.8	0.82	2.04	5.98 ± 0.06	46.79 ± 0.67
	♂ and ♀	12	19.5	0.84	1.99	5.69 ± 0.04	44.91 ± 0.48

¹ Average for 6 mice.

² Average for 12 mice.

($5.11 \pm 0.04 \mu$). The average for both sexes was $5.35 \pm 0.03 \mu$. The follicular diameter in the male was $38.06 \pm 0.53 \mu$, larger than that in the female ($36.45 \pm 0.57 \mu$) but not significantly so. In most of the follicles the colloid stained orange with a light blue periphery; others were filled with light-blue-staining colloid which seemed less opaque than the orange-staining substance and was probably in a liquefied condition, indicating either newly secreted material or colloid in the process of being resorbed.

In the 40- to 41-day-old mice the average thyroid cell height in the female had decreased somewhat ($4.96 \pm 0.06 \mu$) but that of the male had increased ($5.79 \pm 0.07 \mu$). The difference between the sexes was significant as were also the differences between the males and females compared with their own sexes in the younger age group. The follicles were a little larger in the male (average: $40.75 \pm 0.80 \mu$) but remained the same size in the females. Histologically there was no detectable difference in the staining reactions in the two groups.

In the thyroids of the oldest age group (82-83 days) staining reactions were again similar to those in series I and II, but there was a greater variation in the weight of the glands, an increase in the number of the follicles and an increase in the follicular size which was significant in the female but not in the male (table 1). The average cell height had decreased in the male to $5.41 \pm 0.04 \mu$ while that in the female had increased to $5.98 \pm 0.06 \mu$. These figures represented a significant difference between the two sexes and also significant changes from the corresponding sexes in series I and II.

Effects of implanting mouse anterior pituitaries into chicks

Absolute weights of chick thyroids (table 2). The thyroid glands of the chicks 24 hours after implantation of mouse pars anterior varied in weight compared with those of the controls. In series I and III, the average weights for all of the experimental chicks (series I, 3.56 mg., 10 chicks; series III, 3.28 mg., 12 chicks) were higher than those in the respective control groups (series I, 3.17 mg., 2 chicks; series III, 2.53 mg., 4 chicks), but in series II the weight in the 7 experimental chicks (3.47 mg.) was less than that in the 5 controls (4.41 mg.).

Cell height of chick thyroids (table 2). In series I (mice, 26-27 days old), the average thyroid cell height in chicks after the implants of male mouse anterior pituitaries was $2.81 \pm 0.03 \mu$, that after female ones, $2.90 \pm 0.03 \mu$, and that after combining the figures for both sexes, $2.84 \pm 0.01 \mu$. All of these figures represented significant differences from the average height in the controls ($2.50 \pm 0.04 \mu$) and were evidence of a good reaction. The blue-staining colloid and its increased vacuolation were also an indication of stimulation after the pituitary treatment.

In series II, stimulation of the chick thyroid was also very apparent as seen in the vacuolation of the colloid and in the changes in cell height. The average thyroid cell height after the male anterior pituitary implants was $2.34 \pm 0.03 \mu$, after the female ones, $2.39 \pm 0.03 \mu$, and

after male and female implants figured together, $2.36 \pm 0.01 \mu$, compared with an average of $1.99 \pm 0.01 \mu$ in control glands.

The average thyroid cell height measurement of the anterior pituitary-implanted chicks in series III was $3.32 \pm 0.03 \mu$ after male glands, $3.11 \pm 0.03 \mu$ after female ones, and $3.21 \pm 0.01 \mu$ after glands of both sexes considered together. These figures were statistically significant compared with the control average of $2.67 \pm 0.03 \mu$. Here again the

TABLE 2

The thyrotrophic content of mouse anterior pituitaries (AP) as assayed in 2-day-old chicks. (I E, chicks implanted with APs from mice 26-27 days old; II E, chicks implanted with APs from mice 40-41 days old; III E, chicks implanted with APs from mice 82-83 days old. I C, II C, III C, chick controls implanted with mouse brain or left untreated in the respective series).

SERIES	NUMBER OF ANIMALS	MICE		CHICKS				
		Sex	Average weight of AP (mg.)	Average body weight at autopsy (gm.)	Average absolute thy. wt. (mg.)	Average thyroid cell height (μ)	Percentage increase thy. cell ht. over control	Chick units per gm. of fresh mouse AP
I E	7	♂	0.42	36.6	3.57 ¹	2.81 ± 0.03	12.4	295
	6	♀	0.33	39.3	3.55 ¹	2.90 ± 0.03	16.0	485
	13	♂ and ♀	0.38	37.9	3.56 ²	2.84 ± 0.01	13.6	358
I C	2		...	34.3	3.17	2.50 ± 0.04	...	...
II E	4	♂	0.52	34.8	3.43	2.34 ± 0.03	17.6	338
	4	♀	0.40	36.3	3.52 ³	2.39 ± 0.03	20.1	503
	8	♂ and ♀	0.46	35.6	3.47 ⁴	2.36 ± 0.01	18.6	404
II C	5		...	38.3	4.41	1.99 ± 0.01	...	...
III E	6	♂	0.85	39.0	3.44	3.32 ± 0.03	24.3	286
	6	♀	0.82	36.3	3.11	3.11 ± 0.03	16.5	201
	12	♂ and ♀	0.84	37.7	3.28	3.21 ± 0.01	20.2	240
III C	4		...	35.7	2.53	2.67 ± 0.03	...	...

¹ Average of 5 thyroids.

³ Average of 3 thyroids.

² Average of 10 thyroids.

⁴ Average of 7 thyroids.

histological appearance of the glands of the pituitary-treated chicks was one of greater activity than that of the controls, although the glands of the latter were in a more active state than those of the controls of series I and II.

Thyrotrophic potency of the mouse pars anterior in chick units

By utilizing the cell height measurements of the chick thyroids, the percentage increases over the controls after the implantation of mouse

anterior pituitaries were determined for each of the three series (table 2). Then since the average amounts of pars anterior implanted varied, the increase per gram of pituitary was calculated and stated in chick units. The data indicated a greater potency of the female as compared with the male pituitary in the first two age groups and a reversal of this relation in the third. Both male and female glands were more potent at 40-41 days than at 26-27 or 82-83 days of age.

DISCUSSION

According to the assays of the thyrotrophin of mouse anterior pituitaries by the 24-hour chick test, there are considerable differences in its amount with respect to both age and sex. It is evident (table 2) that some increase in potency per gram of fresh pars anterior occurs in both sexes from ages 26-27 to 40-41 days and that the decrease which is seen in both at 82-83 days is much greater in the female than in the male. Such age changes, i.e., an increase from prepuberty to puberty and a decrease by the time sexual maturity is well established, agree in the main with those found by other investigators (table 3). Reece and Turner ('37), assaying the thyrotrophic potency of cattle pituitaries, find that it increases from 26.40 guinea pig units in 1 gm. of fresh gland from calves to 32.13 and 38.36 units in 4- to 10-month-old heifers² and bulls, respectively, and then drops at 11-23 months to 24.59 units in open heifers and 35.02 units in bulls. Data for still older bulls are not given but those for older cows (2 years or more) indicate a distinct difference in thyrotrophin between dairy and beef stocks and also variations in each stock during different reproductive activities. Dairy cows (dry and open) have a thyrotrophic potency of 36.03 G. P. U. which is higher than that for open heifers (11-23 months old) while beef cows (dry and open) have one of 22.53 G. P. U. which is lower. Although Bates, Riddle and Lahr ('35), using percentage increases in the thyroid weights of the immature dove in estimating the thyrotrophin in cattle, state that "Thyreotropic hormone was found in fairly equal quantity in the seven pituitary types [embryos, veal calves, adult steers, adult bulls, non-pregnant cows, cows in early and late pregnancy] with exception that low values were obtained from the glands of embryos (5-7 mos.) and adult steers" (p. 264), when the data of their table 1 are figured on the basis of 1 gm. of fresh pituitary, they conform in part to the findings of Reece and Turner. According to these calculations there would be an increase from 148.6% per gram of calf pitui-

² Well-cared-for dairy heifers are reported to reach puberty at about 7 months (Dukes, '42) which would make the period fall within the group of cattle aged 4-10 months.

tary to 206.0% for non-pregnant cows and 269.6% for adult bulls. The ages of the adults are not given but it seems probable that the last two figures represent full sexual maturity rather than puberty. If so, there may have been a high peak at the latter period.

TABLE 3

*The thyrotrophic potency of the pituitaries of certain mammals.
(AL = anterior lobe; PA = pars anterior).*

	CATTLE Bates et al., '35 (table 1) ¹ % incr. dove thyroid wt. per gm. fresh pit.		CATTLE Reece and Turner, '37 (Sum- mary) guinea pig units per gm. fresh AL		RABBITS Bergman and Turner, '41 (table 2) Bergman-Turner chick units per gm. fresh pit.		RATS Turner and Cupps, '39 (table 1) Bergman-Turner chick units per gm. fresh pit.		MICE Present study Adams- Beeman, '42 (p. 140) chick-units per gm. fresh PA	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Pre- puberty	calves 148.6		calves 26.4		149 gm. body wt. 30.88	163 gm. body wt. 29.75	75.9 gm. body wt. 141	75.47 gm. body wt. 121	26-27 days 295 485	
Puberty	?	?	4-10 mos. 38.36 32.13		2503 gm. body wt. 83.92	2489 gm. body wt. 89.00	129 gm. body wt. 332.8	123.6 gm. body wt. 208.0	40-41 days 338 503	
Early sexual ma- turity	"Adult bulls"	"Not preg- nant cows"	11-23 mos. 35.02 24.59		4128 gm. body wt. 53.27	4021 gm. body wt. 48.80	224.7 gm. body wt. 210.0	226.0 gm. body wt. 127.0	82-83 days 286 201	
Late sexual ma- turity			2 yrs. or older Dairy 36.03 Beef 22.53				274.9 gm. body wt. 174.0	259.0 gm. body wt. 139.0		

¹ Data calculated for 1 gm. fresh pituitary from table 1.

Similarly, Turner and Cupps ('39) report an increase and then a decrease in thyrotrophin per gram of fresh rat anterior pituitary as body weights increase (table 3). The anterior pituitaries of New Zealand White rabbits of approximately 2500 gram body weight also contain more thyrotrophin than those of smaller or larger ones (Bergman and Turner, '41), (table 3). Although neither ages nor stages in the life cycle of the rats or the rabbits are specifically stated, it is probable that the peaks of thyrotrophin in both coincide with puberty. At least a weight of about 130 gm. for male rats and of 110 for females of 70 days

(Jackson, '13) and one of about 2500 gm. for rabbits (Hammond and Marshall, '25) are average figures for this period in these animals. If these data (table 3) for cattle, rabbits, rats and mice are plotted, using prepuberty, puberty, early sexual maturity, and late sexual maturity as points on the abscissa and units of thyrotrophin per gram of fresh

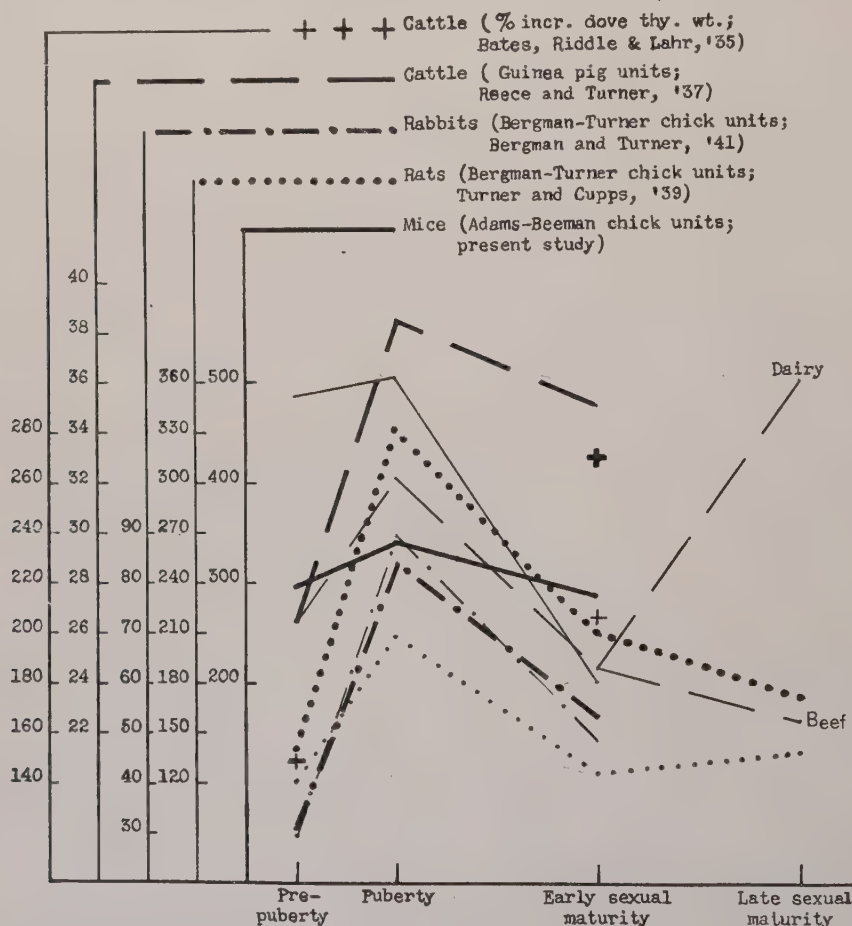


Fig. 1 Graph showing the thyrotrophic content of the pituitaries of cattle (Bates, Riddle and Lahr, '35; Reece and Turner, '37), rabbits (Bergman and Turner, '41), rats (Turner and Cupps, '39) and mice (present study) at prepuberty, puberty, early sexual maturity, and late sexual maturity. For data, see table 3. In similar designs, the heavy line represents data for males; light line, data for females.

pituitary as points on the ordinate, it will be seen that the curves have the same general pattern (fig. 1). Thus in the mouse the peak in thyrotrophin coincides with the period of puberty in the animal and a decrease occurs as the animal becomes older and heavier as it appears to do in cattle, rabbits, and rats and as is also reported for swine (Elijah,

'40, cited by Bergman and Turner, '41). Saxton and Greene ('39), however, find the pars anterior of the immature rabbit more potent in thyrotrophin than that of the mature one, while glands of older females have less hormone than those of young ones. Their data on the thyroid response of the guinea pig to anterior pituitary administration are given in terms of the qualitative histological response and are not defined for a unit weight of pituitary tissue. Only in tests of human anterior pituitaries (Müller, Eitel and Loeser, '35; Saxton and Loeb, '37; Witschi and Riley, '40) differences in thyrotrophin with varying ages have not been found.

In the case of the two sexes, the data for the mice indicate a distinct difference when the thyrotrophic content is expressed in chick units per gram of fresh anterior pituitary tissue (table 3, fig. 1). In the first two age periods examined, the pituitary of the female is more potent than that of the male, but in the last one the reverse is true, although the difference between the two potencies is much less than in the other age groups. Whether this is a permanent shift in the relationship can only be decided when a larger number and still older groups of animals are tested. It is possible that phases of the estrous cycle in the female (which were not considered) may be involved in the changed pattern. At least the suggestion deserves further exploration since a lack of sex hormones has been found to modify the quantity of thyrotrophin in rats (Turner and Cupps, '40). It is interesting, however, that a similar change occurs in New Zealand White rabbits (Bergman and Turner, '41). In these animals, according to the data in their table 2 and figure 3 a gram of the female gland is somewhat more potent than one of the male in all but two weight groups (163 gm. females matched with 149 gm. males; 2032 gm. females matched with 2009 gm. males) up to about 2500 gm. of body weight, but it becomes less potent than the male's as the animals grow heavier. Bergman and Turner apparently do not consider such differences in thyrotrophin in the two sexes significant. In this opinion, they would agree with the investigations of Chen and Van Dyke ('36) and Saxton and Greene ('39) on two other strains of rabbits and also with the tests of human pituitaries and urine made by Aron and Klein ('30), Müller, Eitel and Loeser ('35) and Witschi and Riley ('40). In the other animals so far studied (table 3), however, a gram of anterior pituitary from males is consistently and markedly more potent than one from females (rat: Turner and Cupps, '39; cattle: Bates, Riddle and Lahr, '35;³ Reece and Turner, '37).

³In their table 1, the difference in thyrotrophin appears to favor the female (cows, 103%; bulls, 93% increase in thyroid weight of immature doves). However, on the basis of 1 gm. of tissue, the figures would be 206.0% for non-pregnant cows and 269.6% for adult bulls.

In the present study, measurements of the cell heights and of the follicular diameters of the thyroids of the mice furnishing the pituitaries have also been made as a gauge of thyroid activity and therefore a possible indicator of the release of thyrotrophin from the anterior pituitary. While all of the glands can be said to be fairly active as is characteristic of the mouse (Thurston, '33; Adams and Tukey, '38), it has been found that the average thyroid cell height varies significantly both from age to age and between the sexes in the three groups studied (table 1). Also by 82-83 days, the follicular diameters are significantly larger than they were at prepuberty (cf. Smith and Starkey, '40). Moreover, the pattern in cell height differs in the sexes. In the male, the height rises from $5.11 \pm 0.04 \mu$ at 26.27 days to $5.79 \pm 0.07 \mu$ at 40-41 days and then falls to $5.41 \pm 0.04 \mu$ at 82-83 days while in the female the reverse is true: the height falls from $5.58 \pm 0.06 \mu$ to $4.96 \pm 0.06 \mu$ and then rises to a high of $5.98 \pm 0.06 \mu$. If these figures may be interpreted as indicative of the release of thyrotrophin, while the thyrotrophic content of the anterior pituitary is indicative of the momentary storage of thyrotrophin, it appears that in the male, there is a more balanced release-storage relationship of thyrotrophin than in the female (table 2, fig. 1). At least, the thyrotrophic content and the changes in thyroid cell height do not vary as much in the male as in the female. In the latter at 26-27 days, both storage and release are fairly high; at 40-41 days, storage seems to exceed release; and at 82-83 days, release is relatively greater than storage. As suggested above, other factors may also be involved in the greater variability in the female, especially the possible influence of the sex hormones.

In considering the growth that normally occurs prior to puberty, the rising thyrotrophic potency of the male anterior pituitary associated with an increase in thyroid activity may well be correlated with the increase of weight of 3.1 gm. (table 1) in this sex during the interval from prepuberty to puberty. It is to be expected that similar growth would occur in the females, but the average body weight in the group of females studied at 40-41 days is higher by only 0.3 gm. than in the ones at 26-27 days. Since the storage of thyrotrophin appears to be relatively higher than release judged by thyroid activity in the former, it seems possible that the lack of growth may be due in part to an upset in the normal anterior pituitary-thyroid relationship and that the supply of thyroid hormone was insufficient for normal growth. That the lack of growth in the 40- to 41-day-old females is unusual is suggested by the fact that at 82-83 days the average weights of the males and the females is very similar (males, 19.1 gm.; females, 19.8 gm.). Furthermore the figures

for normal growth in white mice (Robertson, '16) and in C-57 black ones (Green and Fekete, '33) support this suggestion. Robertson finds the peak of a third cycle of growth in early life at 6 weeks followed by a continuous but slow decrease in growth rate in mice of both sexes and the figures of Green and Fekete indicate a similar pattern. Thus in the case of the group of female mice at puberty, the simultaneous study of thyroid activity and of thyrotrophic potency of the pars anterior seems to offer a clue for the interpretation of actual growth data.

SUMMARY AND CONCLUSIONS

1. The thyrotrophic content of the anterior pituitaries of male and female albino mice of three ages was assayed by the 24-hour test in 2-day-old chicks. These assays were then correlated with the activity of the thyroids of the mice as judged by thyroid cell height in an effort to interpret the release-storage relationship of the thyrotrophin in the pars anterior.

2. The thyrotrophin of the anterior pituitaries of mice of both sexes increased from prepuberty (26-27 days) to puberty (40-41 days) and decreased as sexual maturity became fully established (82-83 days). The decrease was greater in the female than in the male gland.

3. The thyrotrophin of the female anterior pituitary was greater than that of the male at 26-27 and 40-41 days, but less at 82-83 days.

4. In the thyroids of the male mice, the cell height rose from prepuberty to puberty and then dropped at early sexual maturity. In those of the female, the reverse of these relations was found.

5. It appears that in the males at the three ages studied, the storing and releasing of thyrotrophin by the pars anterior were more nearly at an equilibrium, whereas in the females at 26-27 days the gland was storing and releasing at a relatively equal and fairly rapid rate; at 40-41 days, it was storing more than it was releasing; and at 82-83 days, it was releasing more than it was storing.

6. There is a possibility that the thyrotrophic content of the pars anterior and the thyroid activity in the group of female mice at 40-41 days have a bearing on the growth of this group. The weight increase from prepuberty to puberty in the females was very small and the coincidence of high thyrotrophin-storage and low thyroid activity suggests a possible lack of thyroid hormone during this period of usually rapid growth.

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SOME ANOMALOUS HAMSTRING MUSCLES

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THREE FIGURES

Anomalous arrangements of one or more of the muscles comprising the hamstring group have been described by numerous investigators, including von Luschka (1865), Wood (1866-67), Macalister (1875), Halliburton (1881), Gruber (1886), Le Double (1897), Bardeen ('06-'07), Moore ('22), Fischer ('26), Seelaus ('27), and Holmgren ('38). Various comparative myological studies, such as those by Leche (1874-1900), Kolesnikow ('33) and Haines ('34), have offered a basis for interpreting some of these variations as reversional, since homologous muscles are found in some of the lower animals. Other variations do not readily admit of such interpretation and it is obvious that more remains to be done on the problem.

In view of the attention variations in these muscles have received it might have been supposed that all important deviations would have been found and recorded, but in the course of recent routine dissections two unusual cases of anomalous arrangements have been encountered. The disposition of the muscles in the first case bears no resemblance to any description previously reported so far as could be determined by an exhaustive search of the literature. The anomalous muscle described in the second case has been reported only once before.

Case 1. On the left side of a white, male cadaver, 84 years of age, the semitendinosus, semimembranosus and long head of the biceps femoris muscles all originated by a common tendon (fig. 1) which was attached superiorly to the sacrotuberous ligament and was continuous with the intermuscular septum which passed cranially to split and ensheath the piriformis muscle. Reinforcing the tendon on its ventral aspect were muscle slips arising from the deep surface of the quadratus femoris muscle, from the ischium between the attachments of the obturator externus and quadratus femoris, and from a line extending transversely for 2.5 cm. on the femur lateral to the intertrochanteric crest. The tendon was not attached to the ischial tuberosity, but was separated from it by a bursa. Distal to its origin it became rounded, measured 13 cm. in length and varied between 7 and 11 mm. in diameter.

Near the middle of the thigh the inferior end of the tendon gave rise simultaneously to the muscle bellies of the semimembranosus, semitendinosus and long head of the biceps. These assumed their normal relations and passed to their insertions in the usual manner. The short head of the biceps femoris muscle was not abnormal either in its origin or in its relation to the long head.

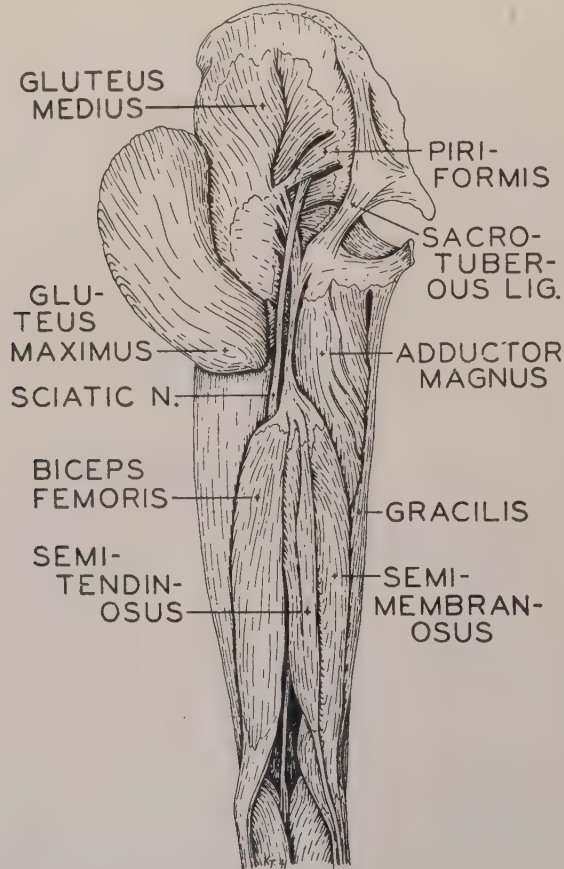


Fig. 1 A sketch of the dorsal aspect of the left thigh of case 1. The gluteus maximus muscle has been reflected to show the common tendon of origin for the hamstring muscles. $\times \frac{1}{2}$.

Three branches from the tibial portion of the sciatic nerve joined the common tendon and became lost in its substance. The nerves to the three muscle bellies arose from the tibial portion of the sciatic at the lower limit of the common tendon. Two of these entered the upper third of the semimembranosus belly while a third branch entered the muscle in its middle third. One branch supplied the belly of the semitendinosus

passing into the muscle in its lower third. The branch to the long head of the biceps femoris entered its upper third.

Inasmuch as a search of the literature has failed to reveal a homologous arrangement of the hamstring muscles in any other species, this anomaly is not regarded as reversional in character. Neither is it

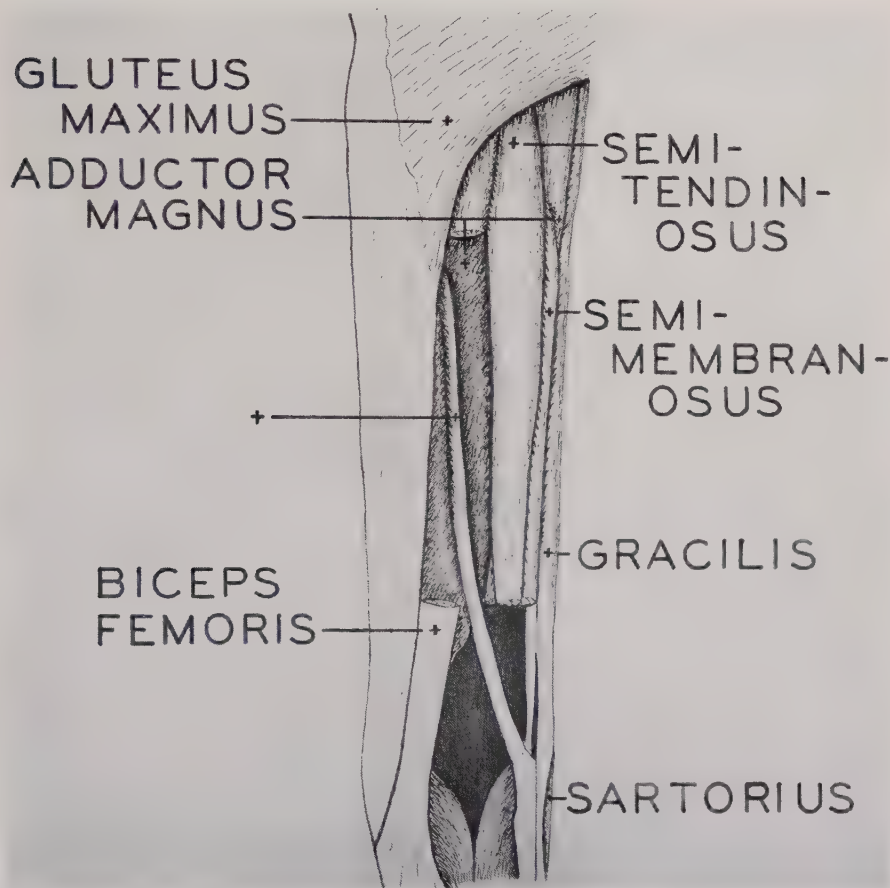


Fig. 2 A sketch of the dorsal aspect of the left thigh of case 2. The distal portions of the semimembranosus and semitendinosus and the intermediate part of the long head of the biceps femoris have been removed to show the anomalous muscle (+). $\times \frac{1}{2}$.

likely that it was "progressive" since there are no known tendencies in that direction. It therefore seems desirable to place it in Huntington's ('01-'02) classification of fortuitous variations.

Case 2. Here a supernumerary muscle occurred bilaterally in the thighs of a white male subject, 44 years of age. On the left side (fig. 2) it originated from the linea aspera, between the origin of the short head

of the biceps femoris and the insertion of the adductor magnus, and from septa between it and these muscles. The bony attachment extended along the femur for a distance of 17 cm. The muscle passed medially and inferiorly behind the popliteal vessels and in front of the long

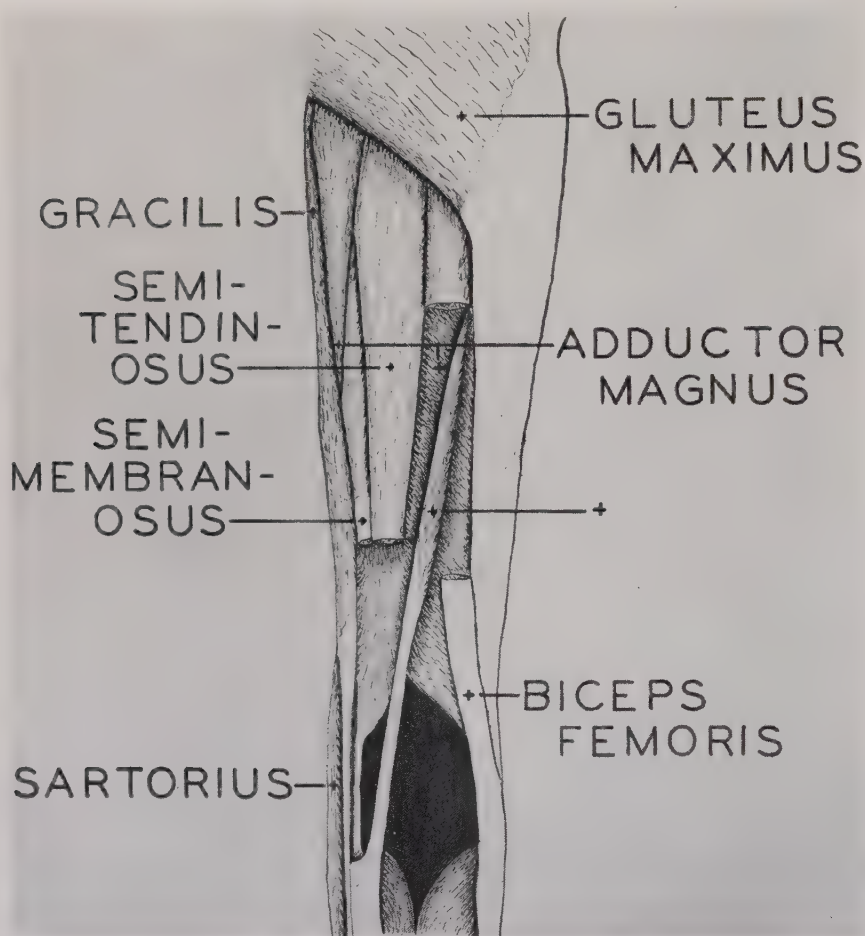


Fig. 3 A sketch of the dorsal aspect of the right thigh of case 2. The intermediate part of the long head of the biceps femoris and the distal parts of the semitendinosus and semimembranosus muscles have been removed. Anomalous muscle at +. $\times \frac{1}{2}$.

flexors of the leg. It inserted into the dorsal aspect of the capsule of the knee joint medial to the gastrocnemius and into the deep fascia covering the medial head of origin of this muscle. Both capsule and fascia were thickened and tendinoid in the region of the insertion.

The muscle measured 28 cm. in length and its greatest width was 1.5 cm. The tendon of origin extended for a distance of 14 cm. along

its deep surface, while the tendon of insertion covered the distal 13 cm. of the muscle dorsally. The sciatic nerve, after giving a branch from its tibial portion to the upper third of the muscle, crossed its posterior surface from medial to lateral side.

The supernumerary muscle of the right side (fig. 3) differed only slightly from that on the left. It was attached to the linea aspera for 21 of its total 29 cm. in length and measured 1.5 cm. in its greatest width. The tendon of origin on the ventral and that of insertion on the dorsal aspect were each 13 cm. long.

Abnormal muscles crossing the popliteal fossa from lateral to medial side are rare in man. Fischer ('26) reported two such muscles occurring in the same subject. One arose from the long and the other from the short head of the biceps femoris.

A muscle quite similar to the pair herein noted was described by von Luschka (1865) as perhaps a variation of the semimembranosus muscle. It arose by means of fleshy bundles from the adductor magnus and from the linea aspera between the attachments of the adductor magnus and short head of the biceps femoris muscles. It was inserted into the medial condyle of the femur and into the dorsal part of the capsule of the knee joint.

Le Double (1897) mentioned the muscle noted by von Luschka but designated it as a supernumerary fasciculus of the semitendinosus rather than of the semimembranosus as von Luschka had reported. Le Double supported his view with the statement that in the majority of birds the semitendinosus is a bicipital muscle, one of whose heads arises from the linea aspera and proceeds medially.

In spite of a failure to unite and insert with the semitendinosus, the anomalous pair of muscles reported here should probably be regarded as femoral heads of that muscle.

SUMMARY

Two anomalous arrangements of the hamstring muscles are described.

1. In one subject the hamstring muscles of the left side all originated from a common tendon which was attached to the sacrotuberous ligament, the femur, the ischium, the quadratus femoris muscle and the fascial sheath of the piriformis muscle. The homology of this muscle arrangement is obscure.

2. In a second subject a muscle bilaterally present originated from the linea aspera and passed medially to insert into the dorsal part of the capsule of the knee joint. This muscle is presumably homologous with the femoral head of the semitendinosus muscle of birds.

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ALKALINE PHOSPHATASE IN THE GOLGI ZONE OF ABSORBING CELLS OF THE SMALL INTESTINE

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ONE PLATE (EIGHT FIGURES)

The relationships between discrete intracellular structures, so clearly demonstrable cytologically, and the vital activities of the cell are among the fundamental problems of cytology and cellular physiology. Specific histochemical methods are supplying important means for the further analysis of cellular structure in terms of specific chemical entities and activities. In the present report it will be shown that the histo-phosphatase method of Gomori ('39) applied to cells of the intestinal epithelium reveals a sharp localization of alkaline phosphatase in the cuticular border and in the Golgi zone of these cells. This enzyme is one of a widely distributed group capable of hydrolyzing monoesters of phosphoric acid (Sumner and Somers, '43). Although certain other epithelia contain alkaline phosphatase in considerable amounts, localization of the enzyme in the Golgi zone thus far appears to be a unique characteristic of the intestinal epithelium.

MATERIALS AND METHODS

Specimens of stomach, intestine and various organs were obtained from the frog, chick (6 weeks), mouse, rat and dog. The chick, mice and rats were killed by decapitation, the frog was pithed, and the dog was anesthetized with nembutal. The mice were fasted 12 to 24 hours. Small pieces 1 mm. to 2 mm. in thickness were quickly removed and stored for 18 hours in about 25 cc. of acetone kept slightly above 0°C. The tissues were subsequently cleared in benzene and imbedded in paraffin, sectioned at 5 μ , and mounted in the usual manner. The method for visualizing the locus of enzymatic activity was essentially that of Gomori ('39), with minor modification by Kochakian ('45). The sections were lightly counterstained with eosin. Corresponding specimens were treated with osmic acid according to the procedure of Ludford ('26) for demonstrating the Golgi apparatus. This report is con-

cerned mainly with the distribution of alkaline phosphatase, but acid phosphatase (Gomori, '41) was studied in a few specimens.¹

OBSERVATIONS

The description which follows is based on observations in the mouse, but, as will be mentioned later, confirmatory observations have been made on other species. The general distribution of alkaline phosphatase in the digestive tract, salivary glands, liver, pancreas, urinary tract, adrenal, prostate, seminal vesicles and endothelium was essentially that found by Gomori ('39), Takamatsu ('39) and Kabat and Furth ('41) and will not receive further comment in the present discussion.

Alkaline phosphatase is present in the epithelium throughout the small intestine, but is more abundant in the duodenum than at more caudal levels. The reaction is much more intense in the epithelial cells directly in contact with the intestinal contents and becomes progressively weaker or almost absent in those situated in the crypts of Lieberkühn. The striated cuticular border is always the most intensely stained portion of the cell (figs. 1, 3, 4, 5, 6). In some instances the border is abruptly demarcated from the underlying cytoplasm (fig. 4), while in others the boundary is somewhat obscured by the presence of phosphatase in the apical cytoplasm (fig. 6).

A most conspicuous locus of alkaline phosphatase activity is situated within the cell body immediately distal to the nucleus. In some instances this locus is visualized as a discrete, sharply limited, irregularly shaped body (figs. 1, 4, 6), while in others the reaction is more diffuse but still definitely localized (figs. 3, 5). The supra-nuclear position is a constant feature in all cases. Corresponding with the general distribution of phosphatase throughout the small intestine, this supranuclear locus of phosphatase activity is larger and more heavily stained in cells directly in contact with the intestinal contents, and becomes progressively smaller and less intense until it is absent or can be identified only as a few small granules in the supra-nuclear region of cells situated in the crypts of Lieberkühn.

Supra-nuclear concentration of alkaline phosphatase was also observed in the small intestine of the chick (fig. 7), rat and dog. In these species a diffuse reaction throughout the cytoplasm was generally found, and this tended to obscure the more intense local reaction distal to the nucleus. Although the pictures are not so striking as in the

¹ I am indebted to Dr. Charles D. Kochakian, of the Department of Vital Economics, for the use of his laboratory facilities in carrying out the phosphatase reactions, and also for the use of sections in which the locus of acid phosphatase activity had been demonstrated.

mouse, they are none the less convincing. Preparations from a frog (kept in the laboratory tank for an unknown length of time) showed a diffuse reaction without supra-nuclear localization.

Localized foci of alkaline phosphatase activity within the cytoplasm were observed in only the absorbing cells of the small intestine. The concentration of alkaline phosphatase in the brush border of the renal proximal tubules is well known. Although the cytoplasm of these cells frequently shows a weak diffuse phosphatase reaction, examination of numerous kidney specimens from frog, chick, mouse, rat and guinea pig has revealed no suggestion of a supra-nuclear concentration.

Topographically, and in many cases structurally, the supra-nuclear locus of phosphatase activity is strikingly similar to the Golgi apparatus as seen after the usual osmic or silver techniques. In the intestinal epithelium of the mouse the Golgi apparatus (fig. 2) and supra-nuclear phosphatase (fig. 1) seemingly occupy identical positions. Alkaline phosphatase in the chick is most concentrated about midway between the nucleus and luminal surface of the cell (fig. 7), and osmic impregnation (fig. 8) shows the Golgi apparatus similarly located in this species. Thus in all species in which a supra-nuclear concentration of alkaline phosphatase has been found, its location within the cell has coincided with that of the Golgi apparatus.

Although the cytoplasm in all of the specimens illustrated appears diffusely darkened, this is mainly due to its photographic properties and not to the presence of alkaline phosphatase. In some instances, however, a weak diffuse reaction does occur throughout the cytoplasm. This is always more intense in the sub-cuticular region where intensely reacting coarse and fine granules are frequently seen (figs. 1, 3, 5, 6). In all tissues the nuclear surface and granules within the nucleus are faintly delineated by the alkaline phosphatase technique. This is in accord with Dounce's ('43) *in vitro* studies of isolated nuclei from liver cells.

In a few specimens stained for acid phosphatase the enzyme appears to be present throughout the absorbing cells, and shows no special foci of activity within the cytoplasm. The distribution of acid phosphatase requires further study.

DISCUSSION

The variability and structural complexity of the Golgi apparatus and surrounding cytoplasm have led many investigators to prefer the less definite term, Golgi zone, for this region of the cytoplasm. From the present observations it seems almost certain that, within the limits

imposed by histological methods, alkaline phosphatase in high concentration is present in the Golgi zone of the absorbing cells in the small intestine of the chick and three mammalian species. Innumerable morphologic studies of the Golgi apparatus (reviewed by Kirkman and Severinghaus, '38) have led to the general conclusion that this structure is intimately involved in synthetic activities within the cell. The finding of a local concentration of alkaline phosphatase in the Golgi zone of the intestinal cells attaches more specific functional significance to this region of the cytoplasm, and distinguishes this type of cell from all others yet investigated. This provides definite evidence that although the Golgi apparatus (osmiophilic) is seemingly comparable in all types of cells, the Golgi zone in at least one cell type has specific properties which are undoubtedly related to the specialized functional activities of the cell in question, and suggests the probability that future investigation will disclose similarly specific properties in the Golgi zone of other highly differentiated cells. The association of this enzyme with a well recognized cytological structure and other distinct cytoplasmic foci (fig. 5) strongly suggests an intracellular heterogeneity of function which is to some extent comparable with the structural differentiation of the cell.

The histological localization of alkaline phosphatase in the proximal tubules of the kidney and in the epithelium of the small intestine (Gomori, '39; Takamatsu, '39) is consistent with Lundsgaard's ('33) suggestion that glucose absorption in the intestine and reabsorption in the kidney involves an intermediate phosphorylated form of the glucose molecule. It is significant that in both organs the luminal surface of the absorbing cells is structurally specialized, and that in both cases these specialized surfaces contain alkaline phosphatase in high concentration. This suggests some fundamental similarity in the absorbing mechanisms of these two epithelia.

The lipids are the only large class of materials which must be absorbed by the intestinal epithelium and not by the renal epithelium. The fact that alkaline phosphatase is concentrated in the Golgi zone of the intestinal cells and not in that region of the proximal tubule cells raises the possibility that the alkaline phosphatase at the former locus may be primarily concerned with the absorption of fats. There is some cytological evidence (Cramer and Ludford, '25) that during fat absorption the Golgi apparatus may be involved in the resynthesis of neutral fat within the intestinal cells; but there is also evidence (Liu, '30) that mitochondria are the cytoplasmic structures primarily concerned

with fat absorption. Wotton and Zwemer ('39) have suggested that visible fat droplets may enter the intestinal cells by phagocytosis. Although the entire question of the relation of cellular structure to fat absorption is unsettled, the importance of phosphorylated intermediates (Bloor, '39) offers the possibility that in the intestinal cells the Golgi zone may be a locus for some phase in the metabolic handling of lipids. From the histological picture it would appear that any absorbed materials passing through the intestinal epithelium must encounter two regions rich in alkaline phosphatase: one in the striated cuticular border and another in the Golgi zone.

It has long been claimed that chemically the Golgi apparatus consists of a union of lipoidal and protein components (reviewed by Kirkman and Severinghaus, '38). A lipoidal property is strongly suggested by the reaction of the Golgi apparatus with osmic acid and its failure to react after extraction with fat solvents (Eastlick, '36). Salazar ('42) believes that the protein component is demonstrated by his "tannin-fer" technique. In the present study, mounted sections of small intestine prepared for the phosphatase method by acetone dehydration were run to water and placed in 2% osmic acid. General darkening of the cytoplasm occurred without specific blackening in the supra-nuclear region. It may be assumed that in these sections the lipoidal component of the Golgi zone had been extracted by the acetone, benzene, and xylene to which the specimens had been subjected. The phosphatase, which remains in the Golgi zone even after the application of fat solvents may represent, or be associated with, a protein component of the Golgi material in these cells. It cannot be stated whether the lipoidal material in the Golgi zone is undergoing modification by the phosphatase or is cooperating with the enzyme by providing an interface for the orientation of substrate or enzyme molecules.

The source of the intracellular phosphatase is unknown. Since the enzyme is presumably a protein, it seems likely that it is produced within the cells in which it is found; and it must be admitted that in the intestinal cells there is no evidence directly opposing the view that alkaline phosphatase is synthesized in the Golgi zone. However, the possibility of absorption from the blood stream or, in the case of the intestine and kidney, absorption from the intestinal or tubular contents might be considered. The finding of alkaline phosphatase in the intestinal and renal epithelium of an 18-day rat fetus makes local intracellular formation of the enzyme seem more likely.

SUMMARY AND CONCLUSIONS

1. A slight modification of the method of Gomori for histological visualization of the locus or alkaline phosphatase activity was applied to tissues of the frog, chick, mouse, rat and dog.
2. The general distribution of alkaline phosphatase in various organs was essentially that described by previous investigators.
3. In epithelial cells of the small intestine alkaline phosphatase is particularly abundant in the striated cuticular border and in a supra-nuclear region corresponding to the Golgi zone in osmic preparations.
4. Localization of alkaline phosphatase in the Golgi zone was not observed in other cell types.
5. This apparently unique characteristic of the intestinal epithelium is undoubtedly related to the specialized activity of the absorbing cells. The importance of phosphorylation in the metabolism of carbohydrates and fats suggests that the Golgi zone in these cells may be a region of particular importance in the passage of these substances through the intestinal epithelium.²

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² Since this report was completed, a paper by Bourne (*Quart. J. Exper. Physiol.*, 1943, vol. 32, p. 1) has come to the author's attention, in which it is mentioned without further comment that in the duodenum of the guinea pig Gomori's phosphatase technique sometimes shows "a dark band across the cell about half-way between the nucleus and the distal edge of the cell." It is also mentioned that in the jejunum a few cells "showed nuclei with black caps reminiscent of the Golgi apparatus." The guinea pig was not included in the present study, but from Bourne's description and figures it appears that his preparations did not show the conspicuous supra-nuclear localization of phosphatase described in the present report. This may be due to differences in technique.

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PLATE 1

EXPLANATION OF FIGURES

Photomicrographs were taken at an initial magnification of $1000\times$, and in reproduction have been reduced to a magnification of $800\times$. An apochromatic oil immersion objective, compensating ocular, and Wratten M plates were used without a filter.

Sections shown in figures 1 and 3 to 7 were treated according to a slight modification of the alkaline phosphatase method of Gomori, which leaves a brown or black deposit at the site of enzymatic activity. The sections were lightly counter-stained with eosin. In all specimens intense blackening occurs in the cuticular border and in the cytoplasm immediately distal to the nucleus. Figures 2 and 8 are from specimens treated with osmic acid according to Ludford's method for demonstrating the Golgi apparatus.

1 Mouse. Small intestine. Alkaline phosphatase sharply localized and appearing as a discrete body in the supra-nuclear region of each cell. A few small "granular" foci of phosphatase activity are present in the apical cytoplasm.

2 Mouse. Small intestine. Osmic. Compare position of blackened Golgi apparatus with supra-nuclear locus of phosphatase activity.

3 Mouse. Duodenum. Alkaline phosphatase abundant but somewhat diffusely distributed in the Golgi zone.

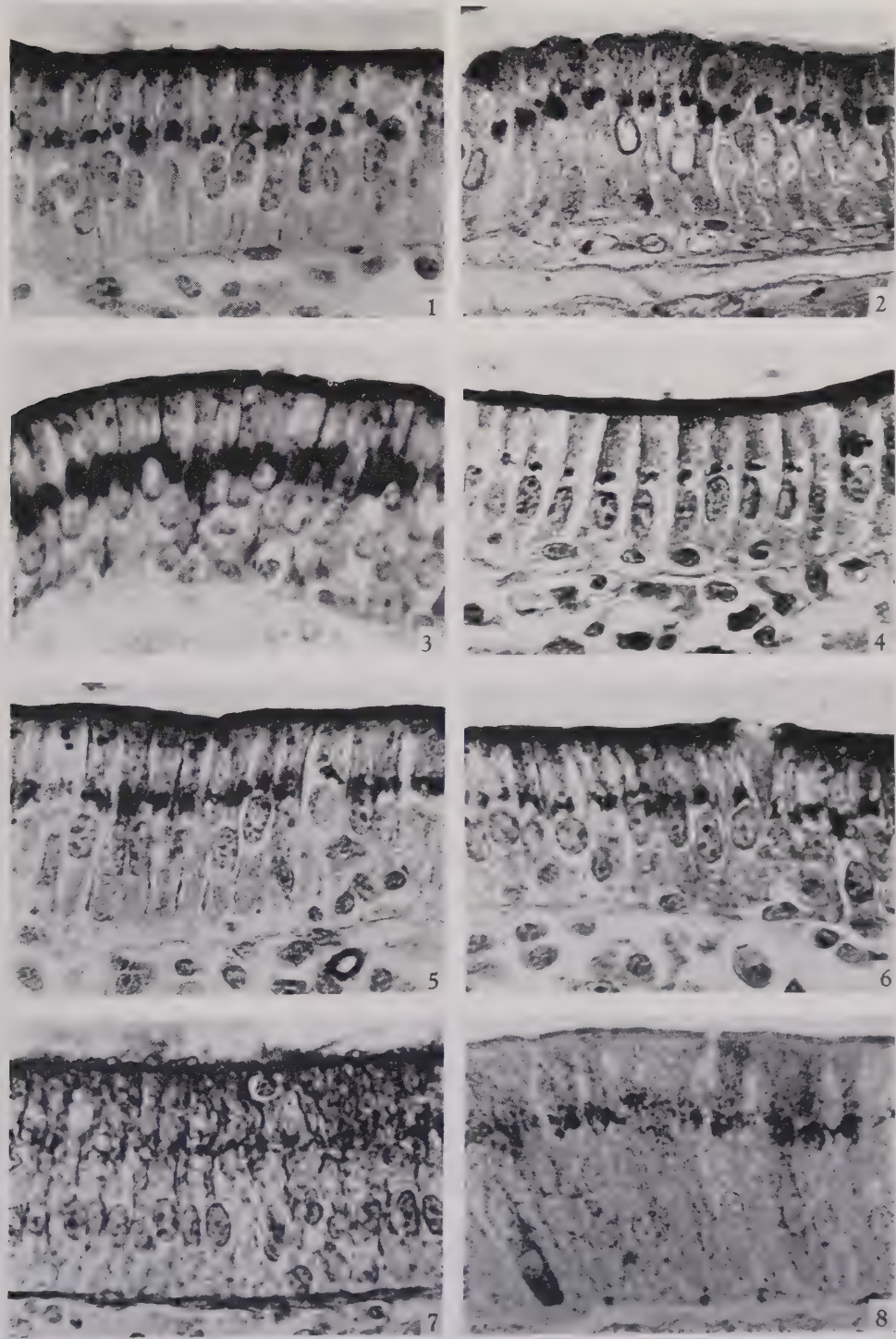
4 Mouse. Lower small intestine. Sharp localization of alkaline phosphatase in the cuticular border and Golgi zone.

5 Mouse. Duodenum. Note "granular" foci of phosphatase activity in the apical cytoplasm.

6 Mouse. Small intestine. Alkaline phosphatase is fairly abundant in the sub-cuticular region. Compare with figure 4. A discharging goblet cell breaks the continuity of the cuticular border. Alkaline phosphatase has not been seen in goblet cells.

7 Chick. Small intestine. Alkaline phosphatase is present throughout the cells but is more abundant in the apical region. Enzymatic activity is particularly intense about midway between the nucleus and cuticular border.

8 Chick. Small intestine. Osmic. Golgi apparatus situated about midway between the nucleus and cuticular border.



THE CARRYING ANGLE OF THE HUMAN ARM AS A SECONDARY SEX CHARACTER

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TWO FIGURES

Considerable interest in the surface anatomy of the human body has been stimulated in recent years by investigations on human constitution. Among the numerous criteria used in determining body type has been the carrying angle of the arm. When the forearm is completely extended and supinated, as in carrying an object, it is not in line with the arm, but is deflected laterally. This lateral deflection has been referred to variously as the carrying or cubital angle.

The lateral deflection of the forearm has been considered as a secondary sex character, since it is generally believed to be greater in the female than in the male. A survey of the literature reveals four papers which have contributed data bearing on this problem: Potter (1895), Mall ('05), Nagel ('07), and Fick ('11). None of these series exceeded thirty individuals except the cases reported by Potter, who unfortunately published only the averages he obtained. Therefore, the present authors believe that it is of value to present the following data procured from a group of more adequate size.

PROCEDURE

Although the carrying angle is primarily the angle which the long axis of the forearm makes with the long axis of the upper arm, it must be more accurately defined for purposes of measurement. This has been done in varying ways by different investigators, in consequence of which the measurements they have obtained are not strictly comparable. Perhaps the most useful method for osteological purposes is to regard the long axis of the humerus as the long axis of the upper arm, and to take the long axis of the ulna as representative of the forearm. This renders the angle independent of pronation and supination. A more rapid method of estimation better adapted to clinical use is the observation of the medial outline of the arm and forearm when the latter is extended and supinated.

The measuring device used in the present investigation is illustrated in figure 1. It consists of a horizontal base to which a vertical board 16 cm. long and 10 cm. high is rigidly attached parallel to the long axis of the base. A second vertical board 49 cm. long is hinged to the first so that it can rotate on the base, allowing the cubital angle to be measured by the angle between the two vertical boards. A scale reading in degrees is marked off on the base board and read by means of a pointer attached to the moveable vertical board.

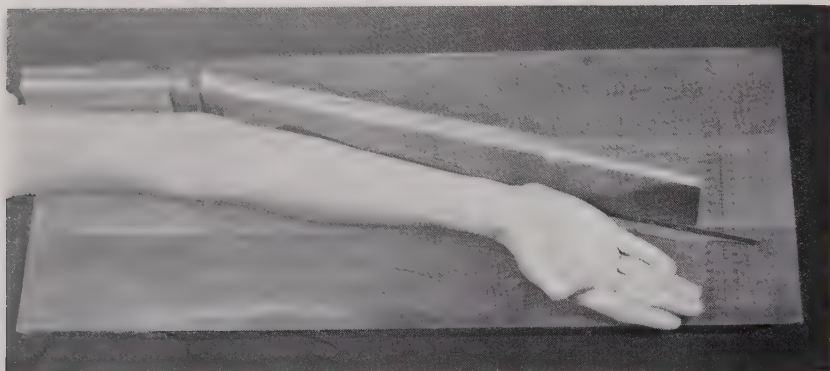


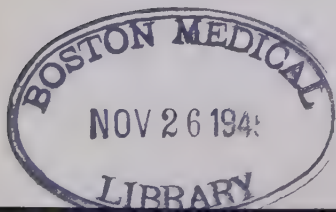
Fig. 1 Photograph of the apparatus used in measuring the carrying angle of the arm.

Measurements are made by placing the right arm of the subject on the horizontal board with the forearm extended and supinated. The prominence of the medial epicondyle of the humerus is placed in contact with the hinge and the upper arm is held lightly against the vertical board. The moveable board is then swung against the medial surface of the forearm so that it is in contact with the prominence of the head of the ulna. The angle of deviation of the forearm can then be read on the scale.

The angle measured was the deviation of the medial border of the forearm from that of the upper arm. For comparison of the present results with those obtained by investigators who recorded the obtuse angle, their values may be subtracted from 180° .

MEASUREMENTS

The carrying angle was measured to the nearest degree on 105 white male medical students and on 112 white female medical and nursing students at Columbia University. None of the individuals in either of these series had a history of trauma in either the upper arm or forearm.



The distribution of the measurements of the carrying angle for both the male and female series is shown in figure 2. In the males, the angle ranges from 3° to 28° , with a mean of $14.4^{\circ} \pm 0.5^{\circ}$. The range in females is from 6° to 29° , with a mean of $16.2^{\circ} \pm 0.5^{\circ}$. The average carrying angle in the female, measured as a deviation from a straight line, is consequently only 1.8° greater than the male.

The variation in the angle is somewhat greater in males than in females. This can be judged approximately from the ranges given above, but is measured more accurately by the standard deviation, which is 5.1° for the male series and 4.8° for the female.

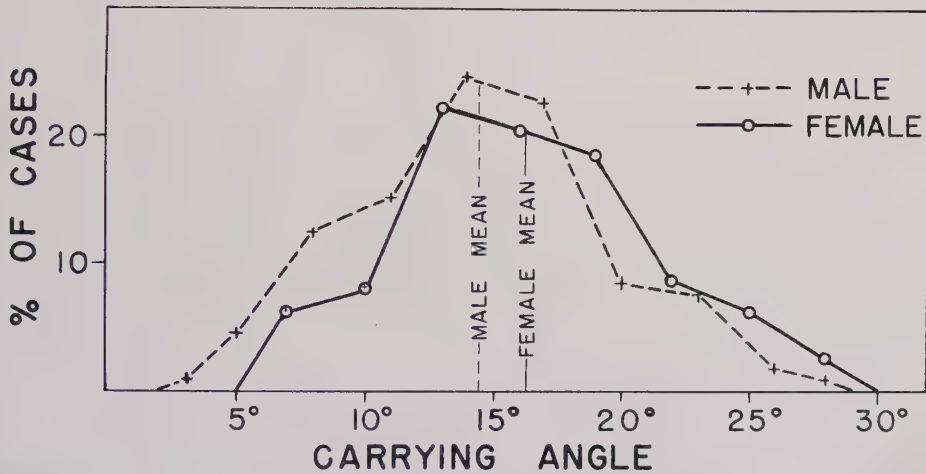


Fig. 2 Distribution of the carrying angle of the arm in a series of 105 males and 112 females. The angle is measured as the lateral deviation of the medial border of the forearm from that of the upper arm.

DISCUSSION

The results of this investigation agree with those of earlier workers in that the deviation of the forearm of the female is somewhat greater than that of the male. The difference of 1.8° found in the present series is considerably smaller than the 5.8° reported by Potter (1895). There is closer agreement between the present results and those of Mall ('05), who found a sex difference of 3.5° for the right arm of negroes. The present data are practically identical with those of Nagel ('07) and of Fick ('11) who obtained differences of 2° .

The difference of 1.8° in carrying angle, as determined in the present series, can be shown to be significant by statistical methods. Although this is of interest, since it allows the cubital angle to be considered

as a minor secondary sex character, the difference is so small that it does not supply a useful criterion for application to individual cases.

While the difference between the means is relatively small, there is a wide range of variation of the carrying angle in both sexes. The extensive overlapping of the range of variation precludes the use of the angle clinically as a secondary sex character.

Although the difference in carrying angle between the male and female is only of statistical significance as a secondary sex character, this does not preclude the possibility that some useful correlation may be found between the variations in this angle and other constitutional characters such as those described by Sheldon, et al. ('40) and Draper, et al. ('44).

SUMMARY

The carrying angle of the arm has generally been assumed to be a secondary sex character in man. Measurements of the deviation of the medial border of the forearm from the medial border of the upper arm were made on 105 males and 112 females. In males the angle ranges from 3° to 28° , with a mean of 14.4° . The range in females is from 6° to 29° , with a mean of 16.2° . Although the difference of 1.8° is statistically significant, it is too small to be of practical value as a secondary sex character in view of the wide range of variation and extensive overlapping of both sexes.

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ARGENTAFFIN CELLS OF THE GASTRIC MUCOSA OF THE RABBIT, GUINEA PIG, MOUSE AND HAMSTER

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TWO PLATES (EIGHT FIGURES)

There appears to be increasing confusion in the literature regarding the presence, number and distribution of argentaffin cells in the gastric mucosa of mammals. This is especially true of the fundic portion. The more recent papers tend to emphasize the presence of these cells in the pylorus, small intestine (especially the duodenum) and the colon. This emphasis has caused many investigators to ignore largely the stomach in studies of the argentaffin cells of the alimentary tract.

Jacobson ('39) states that in the guinea pig and rat argentaffin cells are completely or almost completely absent from the stomach including the pyloric region. Gillman ('42) repeats this statement for the guinea pig and also includes the dog, baboon and Bantu (human) in this category of mammals in which the argentaffin cells are absent from the gastric mucosa. However, Kahlau ('31) described argentaffin cells in the gastric mucosa of the guinea pig and recorded their occurrence as less frequent than in the duodenum and about equal to that of the jejunum. Tehver ('30) reaffirms the earlier observations on the presence of these cells in the gastric mucosa of the dog and has made counts of the numbers present in the fundic and pyloric regions.

Popoff's ('39) illustrations indicate that argentaffin cells are numerous and evenly distributed in the stomach of the rabbit but fewer and limited to particular areas in the human stomach. The silver method employed by him does not appear to be highly selective since he finds that parietal, mucous and Paneth cells may also be blackened by the silver. Cordier ('26) and Kull ('25) appear to be in agreement that argentaffin cells are few and demonstrated with difficulty in the gastrointestinal tract of the mouse and rat.

It is difficult to assess the situation in the mammals referred to above. Often different methods have been used to demonstrate the argentaffin cells and few definite records are given regarding the relative numbers of cells present. Furthermore, usually insufficient areas of the gastric

and intestinal mucosa are shown in the illustrations to enable the reader to form an individual judgment.

Good quantitative data, however, are available for the first 3 cm. of the duodenum of the guinea pig, rat and mouse. In the guinea pig (Hallier, '37; Höschen, '37; Schumann, '39; Schleicher, '39) the average number, based on counts of longitudinal sections, for this region is approximately 1500 in the male and 1700 in the female; in the rat (Klemm, '37; Hallier, '37; Vetter, '37, '38; Münch, '39; Schleicher, '39; Imschweiler, '40), 165 in the male and 200 in the female, and in the mouse (Vetter, '38), 202 in the male and 234 in the female. In all instances there is a significantly greater number of argentaffin cells in the upper duodenum of the female than in the male.

In recent years the method of Masson-Hamperl has been used almost exclusively to impregnate the granules of the argentaffin cells. Dawson and Barnett ('44), however, found that these cells could be consistently and uniformly impregnated by a slight adaptation of Bodian's protargol method developed primarily for the staining of nervous tissue. This modified method appears to be highly selective for the argentaffin cells of the digestive tract, since no other cells of the wall of the stomach or intestine have been found to react with the protein silver. A brief report has already been made (Dawson, '44) of the successful application of the Bodian method to the gastric mucosa of the rat. In this study there was adequate evidence of the presence of argentaffin cells in surprisingly large numbers. Accordingly, it seemed of interest to extend the use of this method to include other common laboratory animals such as the rabbit, guinea pig, mouse and hamster.

All tissues were fixed in one of the fluids suggested by Bodian ('37), formalin, 5 cc., acetic acid, glacial, 5 cc. and 80% alcohol, 90 cc. for 48 hours, and cleared for embedding in cedar oil. The exposure to the protargol solution (24 hours) and subsequent reduction were repeated once. Toning with gold chloride was usually omitted. In the final preparations the argentaffin cells appear deep black on a golden-yellow background.

Since argentaffin cells are uniformly present in the duodenum of all mammals studied, sections of this region were used as controls and were prepared along with those from selected areas of the stomach. In the guinea pig, mouse and hamster, in which the stomach is relatively small, longitudinal strips sufficient in length to include the different glandular regions were taken. In the rabbit, strips, 2 cm. long, were removed along the greater curvature from the pyloric, fundic and cardiac regions respectively.

RABBIT

Argentaffin cells are relatively numerous in the cardiac region of the rabbit stomach (fig. 1). They are usually rounded in form and show little compression from the surrounding tissues. There is a slight tendency for aggregation at the extreme tips of the gastric tubules and they are more regularly distributed throughout the remaining basal half of the mucosa. Only isolated cells appear in the superficial half. In the fundic region (fig. 2) the argentaffin cells appear less numerous and are rather evenly distributed through the deep half of the tubules. They are more irregular in form and consequently frequently appear smaller. The reason for their greater deformation by the surrounding cells is not apparent. Toward the pylorus the number of cells becomes gradually reduced, until the condition shown in figure 3 is reached. This is typical of the relatively extensive pyloric area.

GUINEA PIG

In the cardiac portion of the guinea pig stomach the argentaffin cells are not so numerous as in the fundic region but they gradually increase in number as the latter region is approached. In both locations the cells tend to be aggregated near the base of the mucosa with few cells above the basal one-third (fig. 4). Toward the pylorus the number is progressively reduced until only a few scattered cells are present at the duodenal junction. In all regions the cells are rounded and rarely show evidences of compression.

MOUSE

In the mouse and hamster a large portion of the stomach is lined by a stratified squamous epithelium which is continuous with a similar epithelium of the esophagus. Consequently the cardiac region is small and poorly defined but the argentaffin cells of this region have the same form and pattern of distribution as those of their respective fundic mucosae. In the fundic mucosa of the mouse (fig. 5) the argentaffin cells have in general the same form and distribution as in the rat (Dawson, '44) but they are less than one-tenth as numerous. Cells of the pylorus are typically rounded and are relatively few in number. They seldom appear as numerous as in the pylorus of the rabbit (fig. 3).

HAMSTER

The argentaffin cells of the fundic region of the hamster are relatively few in number in comparison with those of the rat and rabbit, and are rather uniformly distributed throughout the basal half of the

mucosa. The cells are highly irregular in form and are frequently multipolar (figs. 6 and 8). However, in the pyloric region (fig. 7) they are rounded and although reduced in number are slightly more numerous than in the rabbit, mouse and guinea pig.

Argentaffin cells have not been observed in the stratified squamous epithelium of the esophagus of any of these animals or in the stratified epithelium of the stomach of the rat, mouse and hamster. They are, however, uniformly present in the duodenum apparently in the relative concentrations reported previously by several authors. Isolated cells also appear in the glands of Brunner but they are never so numerous as in the intestinal crypts and epithelium of the villi.

DISCUSSION

This brief record of the morphology, number and distribution of the argentaffin cells in the gastric mucosa of four common laboratory animals admittedly adds nothing to our knowledge of the functional significance of these cells, but does demonstrate the readiness and apparent completeness with which such cells can be selectively impregnated by the Bodian protargol method. The underlying factors that influence the form of the cells are not known. One gains the impression from a study of fixed material that they may be capable of independently changing form and may not always be passively molded by the pressure of the cells about them. It is interesting to note that the cells of the fundic mucosa, with the exception of the guinea pig, are the most irregular in form, especially in the hamster, while in the pyloric region they uniformly tend to be rounded.

The relative numbers present in the various regions of the digestive tract are a feature of some interest. Obviously in these animals under discussion, as well as in the rat (Dawson, '44), the cells are much less numerous in the pyloric than in the fundic region, notwithstanding the emphasis placed on the pyloric cells by earlier authors. The varying statements regarding numbers of cells may be due to the varying effectiveness of the silver methods used to demonstrate these cells. Apparently there is no silver method which is specific for these cells and there are also variations in the relative selectivity of the different methods employed. The method of Popoff ('39) apparently impregnates parietal cells, mucous cells and Paneth cells as well as typical argentaffin cells. This more widespread silver reaction has led Popoff to postulate a genetic relationship between the mucous cells and argentaffin cells of the intestine and between the parietal and argentaffin cells of the stomach. He interprets the argentaffin cell as a stage of func-

tional rejuvenation of exhausted mucous and parietal cells. However in the mammals under study the argentaffin cells tend to be aggregated in the basal half of the mucosa, a position in which chief peptic cells are usually relatively numerous and they are almost absent in the superficial half of the mucosa where parietal cells predominate.

There are no statistical data on the absolute numbers of cells found in the gastric mucosa of mammals although there are good data for the numbers present in the first 3 cm. of the duodenum of the guinea pig (1500–1700), mouse (202–234) and rat (165–200). My observations also indicate that there are still less argentaffin cells in the duodenum of the hamster than in the rat. In the fundic mucosa the number of argentaffin cells does not follow this descending order. They are relatively most numerous in the rat and the order of the remaining mammals is probably rabbit, guinea pig, mouse and hamster, although extensive counts have not been made. In the pylorus the number does not vary so greatly among these animals and it would be difficult to arrange them in any precise order. There does not appear to be a good correlation between the numbers of cells found in the epithelium of the fundic mucosa and in that of the duodenum, i.e., in the rat the concentration of argentaffin cells is highest in the fundic mucosa and second lowest in the duodenum.

SUMMARY

The adaptation of the Bodian protargol method, previously used on the stomach of the rat for the demonstration of argentaffin cells, has been applied to the stomachs of the rabbit, guinea pig, mouse and hamster. This method shows that these cells are uniformly present in the stomachs of this group of animals.

In the rabbit, the argentaffin cells are rounded in form and most numerous in the cardiac region; somewhat irregular in form and less numerous in the fundic region, and rounded and relatively sparse in the pyloric region. They are always restricted in distribution to the basal half of the mucosa.

In the guinea pig, these cells are rounded in form in all regions, being most numerous in the fundic region, fewer in the cardiac end and scattered in the pylorus. They are chiefly found in the basal one-third of the mucosa.

In the mouse they are most numerous in the fundus and relatively few are found in the cardiac and pyloric zones. The argentaffin cells are irregular in form in the cardiac and fundic mucosa and rounded in the pyloric region.

In the hamster the cells of the cardiac and fundic mucosa are diffusely distributed through the basal half of the mucosa. They are highly irregular in form and frequently appear multipolar with long, slender, irregular processes. In the pylorus they are rounded in form.

Argentaffin cells are absent from the esophagus of all animals studied and are not found in the stratified epithelium of the stomachs of the rat, mouse and hamster.

This group of animals can be arranged, on the basis of the relative concentrations of argentaffin cells in the fundic mucosa, in the following descending order: rat, rabbit, guinea pig, mouse and hamster.

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EXPLANATION OF PLATES

All figures are photomicrographs of sections ($7\ \mu$ thick) of the stomach, cut vertically to the free surface. In all cases the photographs are oriented so that the base of the mucosa lies toward the left of the plates. Figures 1 to 7 were taken at a uniform magnification of 240 diameters. The entire mucosa is not illustrated since only a few scattered cells are present above the levels shown. Figure 8 was taken at a magnification of 800 diameters. All were prepared by the modified Bodian method, without gold toning.

PLATE 1

EXPLANATION OF FIGURES

- 1 An area from the cardiac region (1 cm. from the esophageal junction) of the stomach from a mature, female rabbit showing the number, distribution and morphology of the argentaffin cells. The number is slightly exaggerated due to the obliquity of the section.
- 2 An area from the fundic region (midway on the greater curvature) of the stomach from the same animal (fig. 1). The argentaffin cells are less numerous, and more irregular in form than in the cardiac region, with less tendency to be grouped basally in the mucosa.
- 3 An area from the pyloric region (2 cm. from the pylorus) of the stomach of the same animal (figs. 1 and 2), showing the relatively small number of argentaffin cells present.
- 4 An area from the fundic mucosa of a fully-grown, female guinea pig showing the typical number, form, and basal grouping of argentaffin cells.

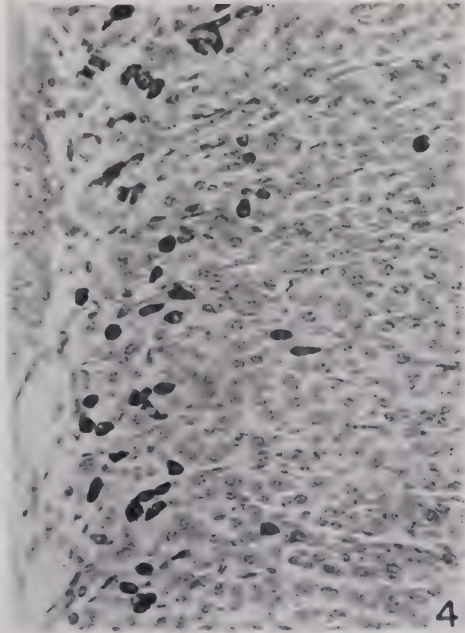
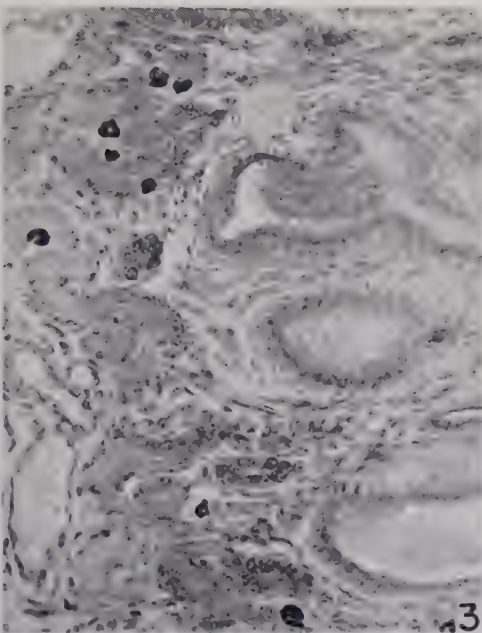
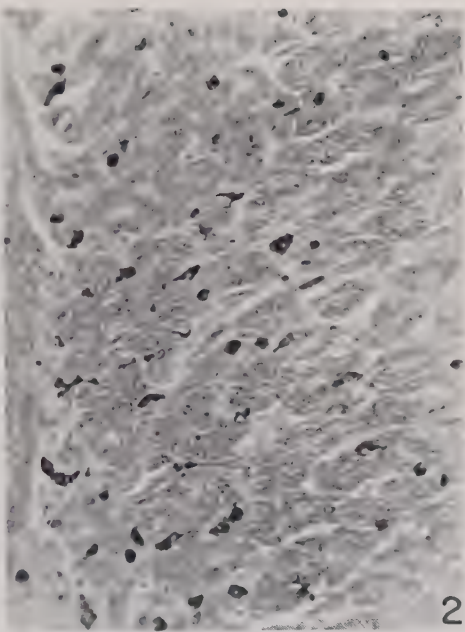
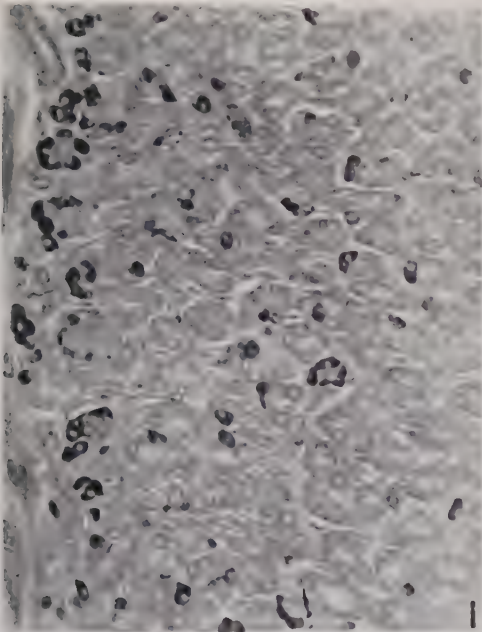


PLATE 2

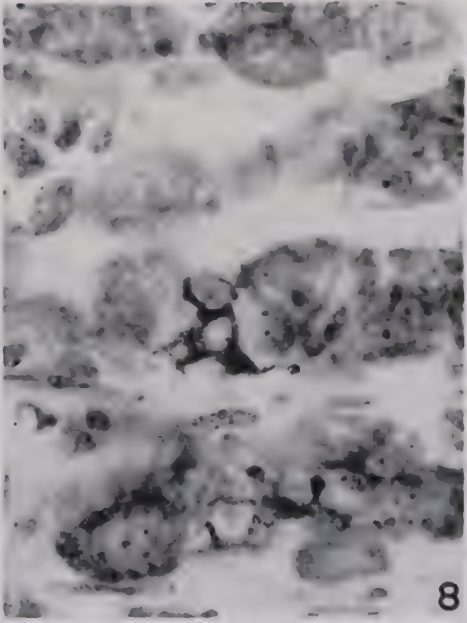
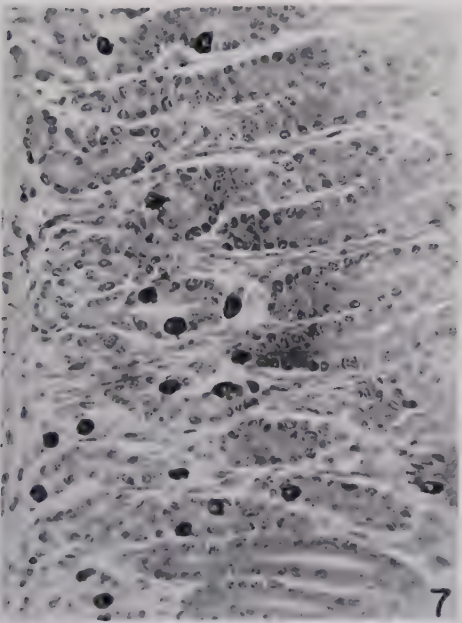
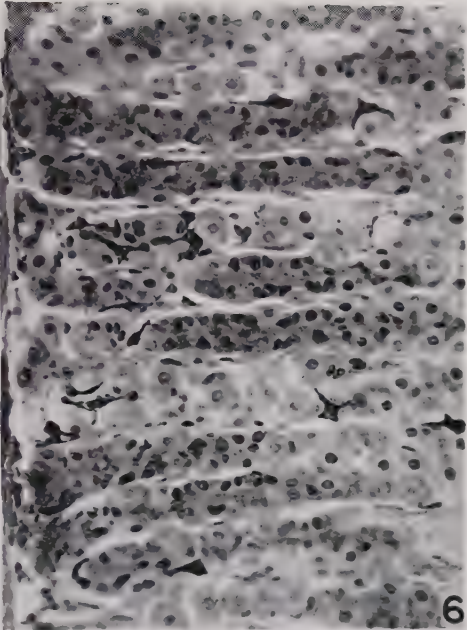
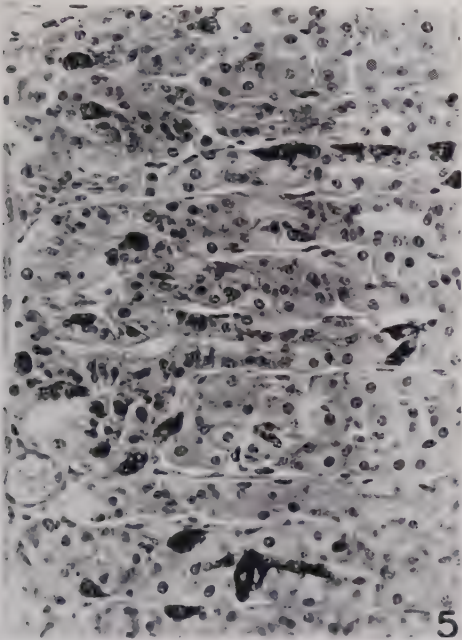
EXPLANATION OF FIGURES

5 An area from the fundic mucosa of a fully-grown, female mouse showing the number, form and distribution of the argentaffin cells.

6 An area from the fundic mucosa of a mature, male hamster showing the diffuse distribution and irregular form of the argentaffin cells.

7 An area from the pyloric mucosa of the same animal (fig. 6) showing the relatively few argentaffin cells which are restricted to a more basal distribution and are rounded in form, in contrast with those of the fundic tubules.

8 Two argentaffin cells from the fundic mucosa of the same animal (figs. 6 and 7) showing their position on the surface of the gastric tubules and the irregular nature of their processes.



THE RELATION OF THE PLACENTA TO THE GROWTH OF THE MAMMARY GLAND OF THE RAT DURING THE LAST HALF OF PREGNANCY¹

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TWO PLATES (EIGHT FIGURES)

The hypophysis, ovaries, placentas and fetuses are known to influence mammary growth during the second half of pregnancy but the exact relationships are not well understood. Hypophysectomy at mid-pregnancy did not affect subsequent mammary growth in rats (Pencharz, '33; Selye, Collip and Thomson, '33; Jeffers, '35), or in mice (Selye et al., '33 a; Newton and Beck, '39; Gårdner and Allen, '42). Removal of the fetuses or the ovaries and fetuses at mid-pregnancy also permitted full development of the mammary gland in rats (Selye et al., '35) and in mice (Newton and Lits, '38), provided the placentas were retained. Removal of the hypophysis and fetuses, on the 12th day of pregnancy, leaving the placentas and ovaries, did not inhibit further growth of the mammary glands in mice (Newton and Beck, '39). Complete evacuation of the uterus during the second half of pregnancy and the insertion of paraffin to distend the uterus failed to prevent involution of the mammary gland (Selye, '34).

Observations made in this laboratory on similar experiments did not always confirm the above results. This report deals with the changes in the mammary gland of the rat which follow the removal at mid-pregnancy of the hypophysis, ovaries, placentas, and fetuses, alone, or in all possible combinations. It will be shown that the placenta plays a unique part in the development of the mammary gland during pregnancy in the rat.

METHODS

Adult nulliparous female rats of the Long-Evans strain, weighing 185-331 gm., were used. Pregnancies were dated on finding spermatozoa in the vagina before 9 A.M. each morning. Body weights were taken at the time of insemination, on the 13th day (day of operation), and on the 22nd day (day of autopsy).

¹ Aided by a grant from the Sage Fund, of the Trustee-Faculty Committee on Research.

Operations upon the genital tract were made through low abdominal incisions. When both fetuses and placentas were to be removed at one operation, the entire uterus was eliminated. To remove the fetuses alone, small incisions were made in the anti-mesometrial wall of the uterus and the embryo sacs were squeezed out. The cut edges of the uterine muscle were brought together by single sutures. Whenever hypophysectomy was to be performed in conjunction with other operations, it was done on the following day (14th day of pregnancy).

At autopsy, the right abdominal and inguinal mammary glands were removed whole, fixed, stained, and mounted on large glass slides. The placentas, adrenals, thyroids, and ovaries were weighed and the sella turcica of each hypophysectomized rat was prepared for histological examination. Only completely hypophysectomized animals are included in the results, although in some cases a very small amount of residual pituitary tissue in no way altered the results from those obtained when hypophysectomy was complete.

For controls, mammary glands were prepared from normal rats on the 13th, 19th, and 22nd days of pregnancy.

RESULTS AND DISCUSSION

In the summary of the results (table 1) it will be noted that in the column of "experimental conditions," only the remaining structures are listed and blanks are left for the organs removed. Observations were made on the degree and amount of lobular and alveolar development in all regions of the glands. In any given rat, it was noted that the inguinal gland always showed more advanced growth than the abdominal glands and hence similar regions of the mammary glands of different rats were compared. It was found that for comparative studies, the anterior portion of the abdominal mammary glands served as an excellent index for the whole gland and could be used almost exclusively. The use of normal glands at the 13th, 19th, and 22nd days of pregnancy for reference controls simplified the estimation of the amount of growth or regression which occurred subsequent to the 13th day of pregnancy in the various experimental groups. All rats gained in weight except those in exp. 19, which lost 14 gm., on an average.

The absence of living fetuses did not influence the development of the mammary gland from the 13th to the 22nd day of pregnancy in an otherwise normal rat (exp. 10). The placentas of the rats in this experiment were markedly smaller than those from normal rats at term, but it appeared that the size of the placenta was not always a criterion of its functional capacity, as will be noted in the table. The ovaries

were of normal size for a pregnant rat. Similar results have been reported in mice (Newton and Lits, '38) and in rats (Selye et al., '35).

When both the fetuses and ovaries were removed on the 13th day of pregnancy, the glands attained a stage of development similar to that on the 19th day of pregnancy and were similar to glands from rats having only their ovaries removed (compare figs. 2 and 5). It should be pointed out that the only inconsistent results in this report occurred in exp. 12, in which two of the six rats failed to exhibit striking mammary growth after removal of both ovaries and fetuses. This discrepancy is unaccountable at present because the placentas apparently were intact and of the same size as the average of the group.

In contrast to the above, removal of the fetuses in hypophysectomized rats (exp. 11) prevented the mammary glands from attaining the growth

TABLE 1

Mammary development on removal of the anterior lobe of the pituitary, ovaries, placentas and fetuses alone or in combination.

EXP. NO.	EXPERIMENTAL CONDITIONS	AV. WT. OF 1 PLACENTA	NO. OF RATS	STAGE OF MAMMARY DEVELOPMENT ON 22ND DAY OF PREGNANCY
		(mg.)		
8P	13th da. preg.	31 (40) ¹	5	Reference controls
8Q	19th da. preg.	362 (21)	3	Reference controls
8J	22nd da. preg.	558 (16)	4	Reference controls
10	A.P. + Ov. + Plac. +	141 (22)	3	Equal to 22nd day of preg.
15	A.P. + ... + Plac. + Fetus.	299 (7)	4	Equal to or slight better than 19th day of preg.
9	 + Ov. + Plac. + Fetus.	433 (33)	4	Equal to 19th day of preg.
18	A.P. + Ov. + +		3	Distinct regression below level of 13th day of preg.
12	A.P. + ... + Plac. +	243 (35)	6	4 slightly better than 19th day of preg.; 2 considerably less developed.
17	 + ... + Plac. + Fetus.	299 (30)	4	Equal or slightly less than 13th day of preg.
11	 + Ov. + Plac. +	125 (32)	4	Equal or better than 13th day of preg., but none equal to 19th day of preg.
13	 + ... + Plac. +	215 (38)	5	Slightly less than 13th day of preg.
16	A.P. + ... + +		2	Severe regression below level of 13th day of preg.
19	 + Ov. + +		3	Severe regression below level of 13th day of preg.

¹ () refers to number of placentas.

that occurred in rats which were only hypophysectomized (compare figs. 3 and 4). It is suggested that the living fetuses in exp. 9 permitted the placentas to reach their functional capacity which resulted in the mammary glands continuing their growth. On the other hand, in exp. 11, in which the fetuses were removed, it is suggested that the placentas were partially functional, and under these circumstances the glands did not grow so well. The mammary glands of rats in exp. 17, in which placentas and fetuses remained, were no different from those of rats in exp. 13, in which only the placentas remained. In both cases, the mammary glands were like those of the 13th day of pregnancy (compare figs. 7 and 8). The fetuses in exp. 17 were all dead and necrotic at autopsy.

An unusual observation was made in exp. 17. Four rats, not included in the table, which were successfully hypophysectomized and ovariectomized became sickly for some unknown reason and either died or were killed between the 19th and 21st days of pregnancy. They lost 25 gm., on an average, in body weight in contrast to similar rats in table 1 which gained 9 gm. on an average. The mammary glands of these 4 rats were equal to or slightly less than the glands of the reference controls on the 19th day of pregnancy. Nonpregnant rats subjected to some types of stress and injected with sex hormones have mammary glands with a precocious or advanced growth of lateral buds and small lobules. For example, in normal rats thyroidectomy (Leonard and Reece, '41; Smithcors and Leonard, '42) and adrenalectomy (Butcher, '39; Reeder and Leonard, '44), and even in pregnant rats, hyperthyroidism (Weichert and Boyd, '34) increased lobular growth. It is suggested that a hormone from the placenta, in exp. 17, while capable of maintaining mammary growth at the 13-day level in healthy rats, was producing advanced lobular growth in the rats that lost weight. Perhaps the absorption of necrotic fetal tissue in some instances caused the untoward condition in these rats.

In exp. 9 in which the hypophyses alone were removed, the mammary glands never exceeded the development found in reference controls killed on the 19th day of pregnancy (compare figs. 3 with 1 and 5). The reports on similar experiments in rats and in mice do not indicate this difference but state that the glands were fully or well developed or gave some milk temporarily, or that the glands were superior to those found at mid-pregnancy (Pencharz and Long, '33; Selye et al., '33 and '33 a; Jeffers, '35; Newton and Beck, '39; Gardner and Allen, '42). As parturition may be delayed several days in hypophysectomized pregnant rats (Pencharz and Long, '33) it might be

that the glands will attain full development (as of the 22nd day of pregnancy), but at a later time.

Removal of the ovaries alone (exp. 15) prevented the mammary glands from growing beyond the stage found at the 19th day of pregnancy. When the hypophysis and the ovaries were removed (exp. 17), the glands did not grow beyond the stage of the 13th day of pregnancy.

When comparisons are made among the various experimental groups it is obvious that of the 4 factors affecting mammary growth, the placenta holds a unique position, for it alone was capable of maintaining the structure of the gland as found at the time of removal of the other 3 factors. Removing all factors except the hypophysis (exp. 16) or the ovaries (exp. 19) resulted in a severe regression of the gland to practically a naked duct system. It was noted also that the average weight of the placentas (exp. 13) increased from 31 mg. to 215 mg. in the absence of the hypophysis, ovaries, and fetuses. Thus it appears that the placenta, by hormonal means, is contributing to the maintenance of the mammary gland between the 13th and 22nd days of pregnancy.

Just as normal growth of the mammary gland in young rats and in rats during the first half of pregnancy has been shown to depend on the combined action of certain hypophyseal and sex hormones (Nelson and Tobin, '36; Reece and Leonard, '41; Cutuly, '41; Lyons, '43), so also it appears that synergistic action among hormones occurs during the 2nd half of pregnancy. The "pituitary-ovarian" regulation of mammary growth during the 2nd half of pregnancy is, by itself, of no great consequence since in exp. 18 there was marked regression of the gland below the level of the 13th day of pregnancy (compare figs. 6 and 7). The "hypophyseal-placental" and "ovarian-placental" relationships are each capable of inducing growth in the mammary gland to the degree found on the 19th day of pregnancy. Unlike results of similar experiments reported by others (Selye et al., '35; Newton and Beck, '39) no glands at the termination of pregnancy in these experiments exceeded in development those found in the controls on the 19th day. To obtain the fully developed mammary gland on the 22nd day of pregnancy required the concerted action of the hypophysis, ovary, and placenta.

These experiments and those of others establish the placenta as an important organ of internal secretion in the rat. Rat placentas and their extracts maintain functional corpora lutea in rats' ovaries (Astwood and Greep, '38; Astwood, '41). The rat placenta secretes a mam-mogen capable of maintaining the mammary gland at approximately

the level of the 13th day of pregnancy for 8 days. The "placental mammogen" plus the ovarian hormones (which the placenta itself may cause to be secreted) synergistically induce growth of the mammary gland from the 13th day to the level of the 19th day. The "placental mammogen" plus some hypophyseal factor also is capable of inducing the same amount of mammary growth. The nature of the "placental mammogen" is now being investigated.

SUMMARY

1. Studies were made of the mammary glands, on the 22nd day of pregnancy, in rats which were subjected to removal, at mid-pregnancy, of the hypophysis, ovaries, placentas and fetuses, alone, or in all possible combinations.

2. The absence of the fetuses reduced subsequent mammary growth only in rats which were hypophysectomized.

3. When the placentas remained and the other factors were removed, the mammary glands were maintained approximately at the level of the 13th day of pregnancy.

4. Combinations of the hypophysis and ovaries, or hypophysis and placentas, stimulated mammary growth to the level found on the 19th day of pregnancy.

5. The fully developed mammary gland was obtained when the hypophysis, ovaries and placentas were present.

6. These results indicate that the placenta of the rat is an endocrine organ and that the active principle(s) work synergistically with hormones of the hypophysis and ovaries to control mammary growth during the second half of pregnancy.

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PLATE 1

EXPLANATION OF FIGURES

The following figures show a part of the right inguinal and abdominal mammary glands, with the latter oriented uppermost in the photograph. Wherever the glands were too large for the slide the anterior tip of the abdominal mammary glands was removed and placed along the side. All glands from experimental rats were killed 22 days after finding spermatozoa in the vagina. (Mag. $\times 2.2$.)

- 1 Mammary glands of a normal pregnant rat on the 22nd day of pregnancy (8J).
- 2 Mammary glands of a rat with pituitary and placentas remaining (12D).
- 3 Mammary glands of a rat with ovaries, placentas and fetuses remaining (9C).
- 4 Mammary glands of a rat with the ovaries and placentas remaining (11B).

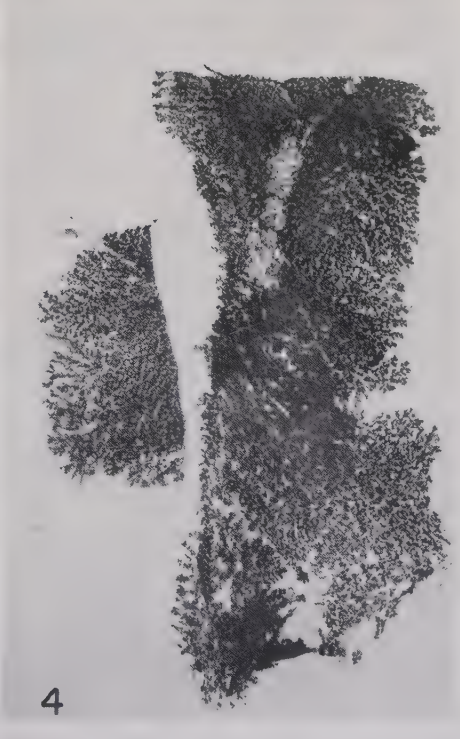
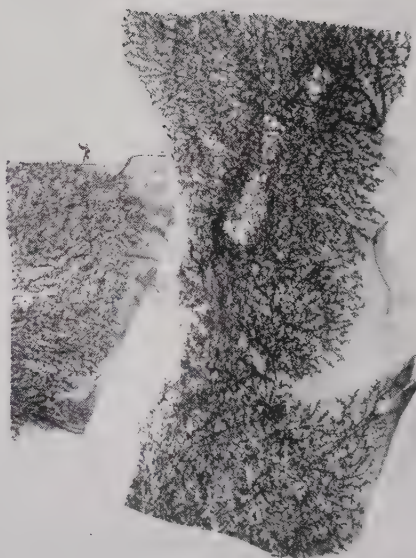


PLATE 2

EXPLANATION OF FIGURES

- 5 Mammary glands of a normal rat on the 19th day of pregnancy (8Q).
- 6 Mammary glands of a rat with pituitary and ovaries remaining (18A).
- 7 Mammary glands of a normal rat on the 13th day of pregnancy (8P).
- 8 Mammary glands of a rat with only placentas remaining (13D).



THE DISTRIBUTION OF POTENTIAL FIELDS WITHIN THE SPINAL CORD¹

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FOUR FIGURES

Previous investigators (Gasser and Graham, '33; Hughes, McCouch and Steward, '37; Barron and Matthews, '38) have studied the "spinal cord potential" by utilizing leads from the dorsum of the cord or from the roots. The first-named investigators have observed that the cord potential evoked by spinal nerve stimulation is repeatable, does not change in sign in response to different afferent sources, is not subject to conditioning, extends beyond the segment stimulated, and is not merely an electrical reflection of the stimulus. In addition to these observations, they have made the following interpretations: that the initial spike represents conduction in the dorsal column, that the longer slower negativity recorded dorsally represents summated activity of interneurons, and that the potentials arise principally in the grey matter. Barron and Matthews have concluded that the potentials represent depolarizing processes different from simple fiber conduction, that they reflect fields of depolarization which affect the activity of the motor neurons, and that they are comparable to afterdischarges in peripheral nerves.

The above observations and interpretations were made by recording potential gradients outside of the spinal cord. A few scattered observations in the literature have discussed the cord potentials from records made within the cord. They have suffered from the defect that histological control of the position of the needle electrodes has not been reported.

As the potential gradients within the central nervous system are signs, and possible regulators, of physiological activity, the following study of the intracordal potentials was begun with the supposition that the central nervous system generally may be so organized as to be more intelligible when the directions, size, and temporal distribution of its potential gradients are known.

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Materials and methods

Cats and monkeys were used in these experiments; dial was the anaesthetic. Laminectomies exposing the lumbo-sacral intumescence were performed and stimulating electrodes placed on the central ends of the cut peripheral nerves. The ventral roots of the segments studied were always cut previous to recording. For needle electrodes, "minuten nadeln"² a special type of fine insect pin was used. These were insulated by baking five coats of enamel on them and the tips opened on a hone when necessary. The electrodes were mounted in a manipulator with vernier calibrations in three planes. Indifferent electrodes and stimulating electrodes were made of silver wire. It was found by experimentation that the records remained identical when the indifferent electrode was moved from one side of the spinal column to the other. It was always kept at the same segmental level as the active electrode and placed on the bone or muscle beside the spinal cord.

A cathode ray oscillograph was used. The push-pull amplifier was condenser coupled with a long time constant. The stimuli were delivered by a multichannel sweep-synchronized stimulator and consisted of brief, single condenser discharges to the tibial nerve.

The procedure used in making the contour maps (for which the term electroarchitectonic maps is suggested) was as follows. The segment of the cord under study was sampled by making upwards of ten needle tracks. In each of these, records were taken at regular intervals (0.3 or 0.5 mm.) as the needle was withdrawn. The result was a family or column of related potential traces for each needle track (fig. 1). The spinal cord was then removed, fixed, sectioned and stained. The needle tracks were indentified from a diagram kept during the experiment and drawn on a camera lucida outline of a section of the cord. The extent of the track was divided by the number of needle stops from which the records were made. Dots were put in the presumptive location corresponding to each trace (fig. 2A).

The potential curves were transferred to coordinate paper with the use of a projector, and the instants to be represented by the maps were chosen. In the accompanying series, these were 1.6, 2.0, 3.0, 3.6, 4.3, 5.0, 6.5, 8.6, 11.3, and 18.5 msec. The voltage deviation of each potential at each chosen moment was then "read" in arbitrary units. On tracings of the master diagram of the spinal cord showing the presumptive location of each station, all of the values for one moment were written in

² Clay Adams.

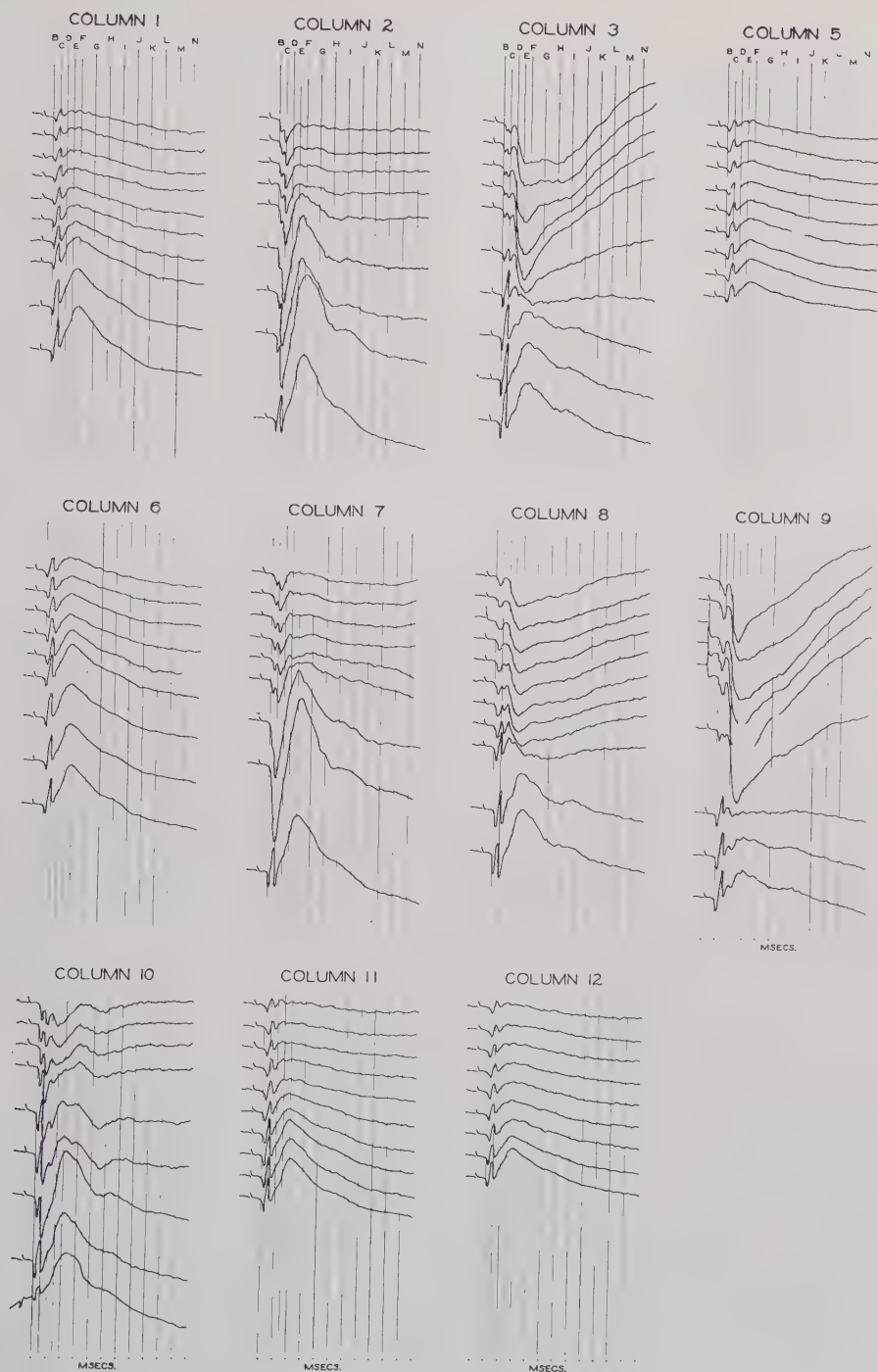


Fig. 1 Families of potential curves recorded in varying depths in eleven needle tracks in the first sacral segment of a cat. The stimulus was a single shock delivered to the tibial nerve. In each instance the potential recorded from the deepest part of the needle tracks is first in the series, that from the superficial surface last. The vertical lines indicate the moments represented in the maps of figure 2. Time in milliseconds.

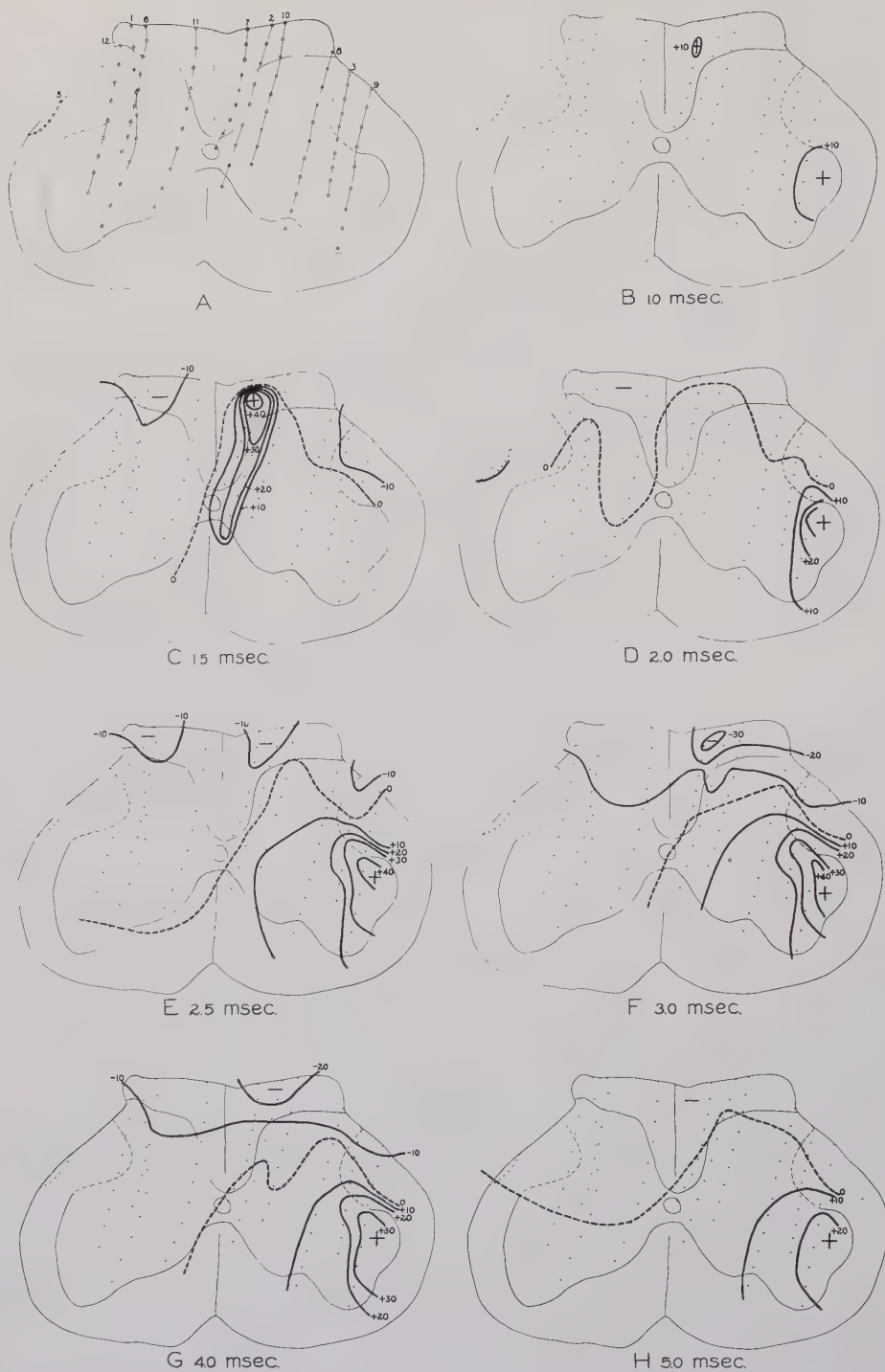
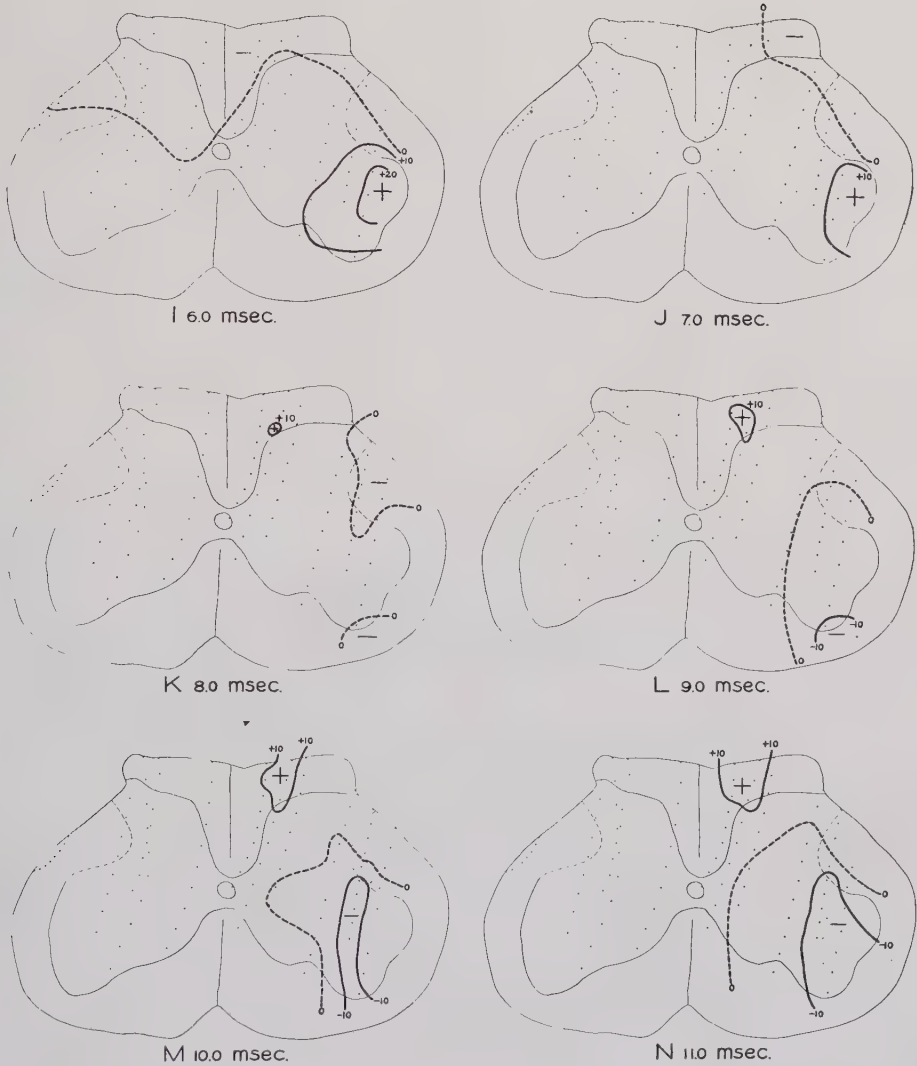


Fig. 2 Series of maps of the potential fields of the spinal cord based on the data of figure 1. A. Schema showing position of needle tracks and stations. B. to N. Contour maps of potential fields in arbitrary units of voltage.



their proper position and iso-potential contours were drawn according to ordinary cartographic technique (fig. 2B-N). With the use of proportional interpolation contours can be drawn with considerable accuracy with the number of points involved. The only contour line with which difficulty was had was that of zero potential. This difficulty is of course inherent in the fact that when little or no activity is occurring, the potential gradients sought by the contourer do not exist. The position of the zero contour is less significant than the other lines in any such map and is accordingly entered as broken lines in figure 2.

One hundred and three potentials were used as a basis for the maps in figure 1. Maps have been prepared with as many as 200 stations with no great increase in accuracy. The fairness of the sampling, in other words, the evenness of the distribution of the stations, is a limiting factor and certain experiments have been unsatisfactory in the mapping because of this.

The possibility that damage from the needle tracks might interfere with the normal production of potentials or reflexes in the segments perforated by the electrodes was considered. Experiment showed that reflex activity of these segments survived with little change and that the order in which the tracks were made had no perceptible effect on the potentials. This is to be accounted for by the small volume of tissue killed by the electrodes and by the large margin of safety in the spinal cord mechanisms.

In all, five cats and two monkeys were used in experiments each of which resulted in at least one complete series of maps. In some of these, the motor cells on one side had been altered by retrograde degeneration, a report of which will be published elsewhere. The project has, at this stage, involved the analysis of 13,876 readings of 1038 separate potentials distributed along fifty-four needle tracks. A degree of familiarity of the potential fields of the spinal cord, acquired in making the maps, enables one to recognize the position in the cord from which a given potential to the stimulus used was taken and to detect deviation from the usual potentials. The logical sequel of these studies is the preparation of more detailed maps of restricted regions of the nervous system.

THE POTENTIALS OF THE SPINAL CORD

1. The dorsal column potential

There are two separate and distinct potential fields which develop in the spinal cord following peripheral nerve or root stimulation. The earliest one to develop is that of the primary afferent fibers or the dorsal column potential. It consists of two components, a spike and a slow wave. The spike potential, so called because of its identity with the spike potential of the literature (Gasser and Graham '33) is detectable in all regions of the cord. Because of its low amplitude it is poorly represented on the contour maps. In the dorsal columns it is generally recorded as a triphasic wave, somewhat distorted, the main or center phase negative. The third phase is rather deficient, being represented by the notch between the center part and the slow potential. At the region of the dorsal column where the active afferent fibers are con-

centrated, the characteristic potential of the injured fiber is recorded, a deep positive potential. On the edges of the region showing this positivity the potential trace bears a peak of negativity often superimposed on much stronger positivity (fig. 1). Though this is a potential of the fibers, hence white matter, the contours demarking it jut into the gray matter in the medial part of the dorsal horn. Here, figure 3, are seen the heavy bundles of myelinated fibers issuing from the dorsal



Fig. 3. Photomicrograph of dorsal horn of spinal cord showing position of needle track corresponding to the fourth station of column 10. The needle track is seen to interrupt branches of the primary afferent fibers passing into the gray matter. Iron hematoxylin stain.

column and ramifying the cellular part of the cord. The potential fields radiate from these fibers as well as from the dorsal white column. In the ventral horn, and lateral and ventral white columns, the spike potential is recorded as a positive wave of low amplitude.

The second component of the dorsal column potential shows by its distribution that it is an afterpotential of the primary afferent fibers. It is recorded everywhere in the dorsal column as a slow negative wave reaching its crest about 2 msec. after the spike and continuing on for

4 or 5 msec. longer. It reaches its greatest amplitude where the spike was recorded with the greatest positivity — in other words, where the concentration of active primary afferent fibers is greatest. It is lost quite abruptly as one passes out of the dorsal columns except in the medial region of the dorsal horn (fig. 2) where the large fibers running into the gray matter show the potential.

These observations support the thesis of Barron and Matthews (*loc. cit.*) that the negative potential following the spike, which is alike observed by their methods or by records made with surface electrodes on the dorsum of the cord, is generated by the dorsal root fibers themselves. They ingeniously explained the potential as arising at the terminations of the fibers, linking its appearance with the increasingly small caliber at that region. With this finer localization my results do not agree. The distribution of the potential shows it to be characteristic of the dorsal column fibers, which are not terminal arborizations. The potential is not found in the neuropil of the gray horns where the afferent fibers presumably reach very fine caliber by branching. The spike potential is but slightly affected by preceding activity except at intervals of less than 2 msec. Closer than that, it shows diminution though it is not certain whether the “conditioning” occurs at the point of stimulation, at the site of the recording or in some region between. The dorsal column potential, however, is greatly diminished by the preceding activity at intervals up to 10 msec. The records show that the positive trough following the cord potential becomes greatly increased by repetitive stimulation, but its nature was not investigated.

It is not certain from our investigation nor from those of others who have described the potentials of the spinal cord that the dorsal column potential is limited to fibers which have carried the spike potential or impulse. Should some or all of the potential prove to be due to reactance of fibers which are neighbors of the “active” fibers, it would be tempting to ascribe the generation of the dorsal root reflex of Toennies ('38) to this mechanism. It may be queried whether the negative after-potential ascribed to the peripheral nerves is not likewise possibly related to fibers neighboring those conducting impulses.

2. The anterior horn potential

Commencing about 0.5 msec. after the onset of the spike potential of the dorsal column a positive potential develops which centers about the dorso-lateral region of the ventral horn. The potential is characteristic of the ventral horn and is closely related, in a manner discussed below, to the firing of the motor neurons and will be hereafter referred

to as the ventral horn potential. It reaches its greatest height very rapidly (fig. 1, 2) and slowly decays for 7 or 8 msec., finally going over to a negativity.

The relation of this potential to the firing of the motor neurons becomes clearer when its first derivative is compared with the ventral root record. Figure 4 shows that the ventral root potential closely resembles

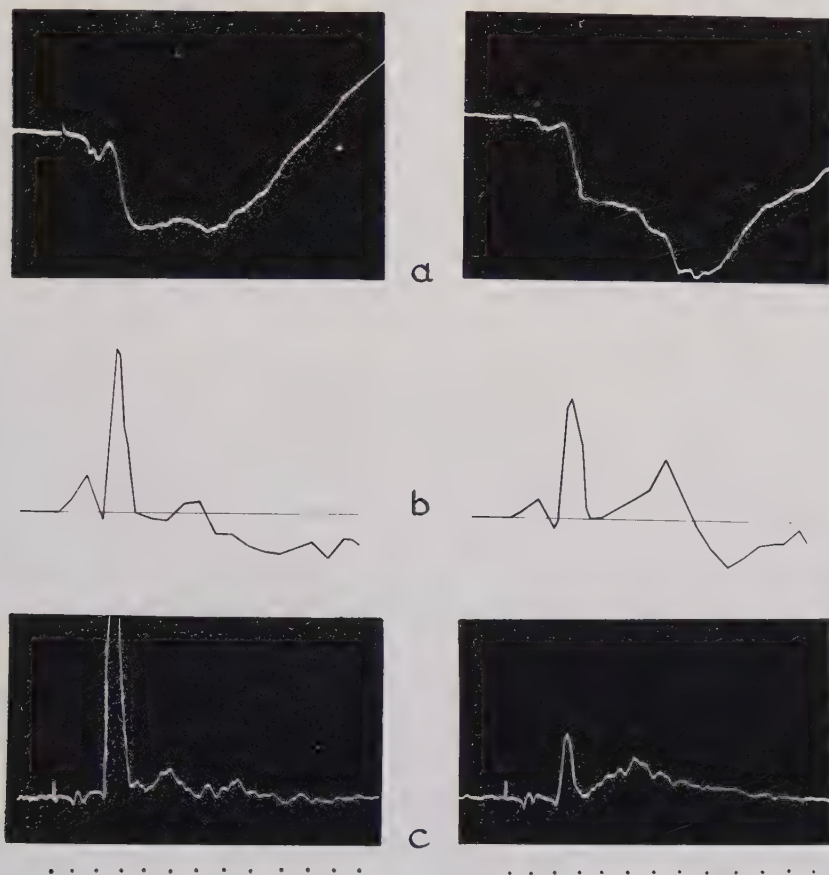


Fig. 4 Ventral horn potentials of a cat evoked by stimulation of tibial nerve. On the right side the nerve had been cut incompletely below the point of stimulation 2 weeks previously. A. Ventral horn potentials in site of greatest deflection. B. First derivatives of ventral horn potentials. C. Potentials of first sacral ventral roots. Time in milliseconds.

the first derivative of the ventral horn potential. The firing of the motor neurons occurs during the periods in which the positivity is increasing. The animal from which these records were taken was a particularly favorable subject for this study in that the right tibial nerve had been sectioned 2 weeks previously and though conduction across

the lesion indicated the section was incomplete, the segmental reflex was still somewhat deficient in the proprioceptive component on the affected side (5, 6). The largest ventral horn potential on each side was accordingly differentiated by the graphical method of Running ('37). Comparison of the resulting derivative with the ventral root potential, figure 4c, shows that the two are closely similar in each instance. This indicates that the motor neurons do not simply sample the chemical milieu within the ventral horn after the manner of counters. Instead they react by firing only to the conditions indicated by increasing positivity and the total of their firing is roughly proportional to the rate of increase.

Before the implications of the above facts are considered, the time relation of the potentials of figure 4 may be noted. The ventral root outflow follows the changes in the ventral horn potential with a very slight time lag—not of the order of magnitude of 0.5 msec. Thus the so-called “synaptic delay” must occur previous to the onset of the ventral horn positivity. Between the mid-point of the spike potential of the dorsal column (fig. 4) and the onset of the positive deflection in the ventral horn (at 1.9 msec.) is a period of time (0.5 msec.) apparently occupied by the conduction of the volley of impulses along the fine collaterals of the primary afferent neurons. This distance is about 3 mm., making the average speed of the order of magnitude of 6 meters per second, a figure within expected limits for fine myelinated fibers. That “synaptic delay” may be ascribable to the afferent fibers has been suggested by Lloyd ('44) and these data support such a supposition.

The question arises as to whether the ventral horn positivity is the summated activity of the motor neurons, of the afferent endings, or of both. In the course of the exploration of the ventral horn, spike activity, apparently potentials from the motor neuron cell bodies, was encountered. As they were of much smaller magnitude than these overall potentials evoked by maximal stimuli (showing 5% or less of the height of the ventral horn potential with the micro-electrodes used in this study) they do not appear in figure 1 or figure 4. The sign of these spikes was not constant, being negative, negative-positive, or positive, and it seems improbable that they would summate to a positive slow potential such as that under consideration. A detailed analysis of the relation of spike activity in the ventral horn to the larger potential will be reserved for a later communication.

DISCUSSION

The method described above, which yields overall views of a spinal segment at chosen moments following stimulation, raises in an acute

form the problem of the origin of the electric potentials of the nervous system. Within the central nervous system, two types of potential have been distinguished. One is the positivity, presumably due to injury of fibers, recorded from tracts of large myelinated fibers (Grundfest and Campbell, '42), and the other, the bipolar field surrounding a collection of activated neurons (Bishop and O'Leary, '42). To this is added, in the preceding pages, a third type—the negative afterpotentials of the dorsal column fibers. The early positivity of the ventral horn reported here is as yet unsolved. It is probable, though not certain, that it is “presynaptic” in nature. Whether it is comparable to the tract potentials mentioned above, depending upon the injury of the neuropil as tract records seem to depend upon injury of the larger fibers, cannot yet be told. If so, little information save the concentration of active units and the time of onset of activity will be gotten from this potential. The possibility must not be overlooked that the boutons themselves generate the potential in some way specific to their functioning.

SUMMARY AND CONCLUSIONS

1. A method is described by which a series of contour maps may be made of the potential fields of the spinal cord at chosen intervals following a stimulus.
2. The distribution in time and space of the principle potentials following tibial nerve stimulation is described.
3. The “negative cord potential” is shown to be an afterpotential of the primary afferent fibers of the dorsal column.
4. A potential characteristic of the activated ventral horn is described.
5. The first derivative of the ventral horn potential parallels the potential of the ventral root. From this it is concluded that the motor neurons show a high degree of adaptability.

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THE INFLUENCE OF SEX AND BREEDING ON SKELETAL AGEING OF MICE ¹

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TWO PLATES (SIX FIGURES)

Skeletal growth proceeds at different rates in different strains of mice. Moreover, in strain C57 the bones of females develop more quickly than those of males, and the osseous tissues of breeding females more rapidly than those of virgins. (Silberberg and Silberberg, '41 a). It was, therefore, thought possible that sex and breeding might influence skeletal development and ageing in other strains also. In order to obtain more definite data on this problem, we examined the age changes in the bones of non breeding and breeding females of various strains. We compared them with one another and with those seen in males of corresponding strain and age.

MATERIAL AND METHODS

One hundred forty-seven mice over 4 months of age and belonging to the closely inbred strains C57, Old Buffalo, CBA, New Buffalo, A, C3H and D were arranged in groups, each containing as many males, virgins and breeding females of the same strain and age as were available. Details are given in table 1.

At necropsy, the upper part of the tibia and the lower part of the femur together with the kneejoints were removed as a whole. The specimens were prepared for histological study according to the method described previously (Silberberg and Silberberg, '41 a).

HISTOLOGICAL EXAMINATION

Before stating the findings in the various groups, we may summarize some general observations on skeletal ageing: Ageing of cartilage is indicated by decreased proliferation of the cartilage cells and by increased degenerative processes, affecting cells as well as matrix. The

¹ The material for this investigation was collected in the Laboratory of Research Pathology, Washington University, Saint Louis, Missouri.

We wish to express our appreciation to Dr. Leo Loeb for his interest and many helpful suggestions in this series of investigations.

cells undergo gradual atrophy or break down more rapidly, and finally they disappear. In the intercellular ground substance, regression manifests itself in either swelling or hyalinization and calcification. Hyalinization is usually spread diffusely throughout the epiphyseal disk, or it may cause the formation of small hyaline wedges between the cartilage cell rows. These hyaline areas show a tendency to metaplastic ossification. Bone thus formed seems to be markedly resistant to perforation by bone marrow, and the osseous plate remains therefore intact well into the second year of life. However, it undergoes progressive thinning, and if the animal lives long enough, the thin bone may yet be resorbed, and complete epiphyseo-diaphyseal union may ensue.

The second mode of regression of cartilage is characterized by a rapid but localized destruction of cells leading to the appearance of "plugs" of degenerated cartilage. This amorphous material becomes calcified and shows many cracks. Eventually, the plugs may ossify or become incorporated in the bone that has replaced the growth zones. At the time, when the resorptive processes begin to predominate, these plugs often become the site of localized perforations of the epiphyseal plate by bone marrow. In some instances, these perforations widen with advancing age; in others, they remain stationary for many months or even for life.

In a number of ageing mice, the articular cartilage undergoes changes which vary in degree from slight hyperplasia and hypertrophy to lesions comparable to osteoarthritis.

A. Changes in the growth zones

1. *Strain C57 (ageing at a slow rate).* Five groups of animals 7, 10, 15, and 20 to 25 months old were examined.

At the age of 7 months, the epiphyseal disks of the males contained more and better preserved cartilage than those of the female breeder, whose growth zones were already markedly hyalinized.

Towards the end of the first year of life, moderate amounts of calcified cartilage were still present in both males and females. Few and small plugs of disintegrated cartilage were noted in the male, whereas in the female these areas of degeneration were larger and more numerous. One breeding female even showed a perforation of the epiphyseal disk.

At 15 months of age, degeneration of cartilage had made progress in all mice, but in the males more than in the females. Thus, conditions in both sexes resembled each other more closely than at the earlier stages. The growth zones had been broken through in both virgin and

breeding females, whereas in the male, the epiphyseal plate was still intact.

In the oldest age group, there were only traces of cartilage left in the male, and wide communications connected the epiphyseal and diaphyseal marrow cavities. In the corresponding female on the other hand, more cartilage was found, and the perforations in the plate were smaller than in the male.

II. Strain Old Buffalo (slowly ageing with marked bone-forming tendency). Three groups of animals 10, 14, and 18 to 21 months old were examined.

In the 10-month-old virgin, the growth zones revealed considerable amounts of cartilage. The cells were atrophic, and the areas of degeneration were limited in size and showed only little ossification. In the male on the other hand, there was less cartilage remaining, and it contained many large calcified and ossified plugs of degenerated tissue. The growth zones failed to show perforations in either the male or the virgin female.

At 14 months of age, the greater part of the growth zones had been resorbed in the male. By contrast, in the epiphyseal disks of virgin females the cartilage cells were more abundant and better preserved; there were only a few small areas of degeneration, and the resorptive processes had just begun to predominate. The breeding female on the other hand, had more extensive degeneration and ossification of the cartilage than the virgin female, but perforations of the epiphyseal plate could not be detected in the breeder.

At the age of 18 months and over (plate 1), all males presented an advanced degree of epiphyseo-diaphyseal union with only traces of cartilage left (fig. 1). In the breeding female the cartilage had undergone further degeneration and calcification as compared with the earlier stages, and perforations were now noted in the growth zone (fig. 2). The latter were, however, not as wide as in the male of corresponding age. The bones of the virgins (fig. 3) had aged only slightly in comparison with those in the preceding stage, and no breakthrough of the plate had occurred.

III. Strain CBA (slowly ageing). Four groups of animals 12, 15 to 16, 19 to 20, and 23 to 30 months old were studied.

At the end of the first year of life, there was still much cartilage present in both sexes. However, the male showed more hyalinization of the matrix, whereas in the corresponding breeding female calcification was more pronounced and a perforation of the plate was being initiated.

The ageing processes in the latter were, therefore, somewhat more advanced than in the male.

At the age of 15 to 16 months, the growth zones of both virgin and breeding females were broken through, whereas in the male they were ossified, but still intact.

At the age of 19 months, almost all cartilage had disappeared in the male, and epiphyseo-diaphyseal union had occurred. In the females, on the other hand, some cartilage was still seen; the virgin female now had wide perforations of the growth zone, whereas in the breeding female these were lacking.

The oldest group consisted only of males; in two of them the epiphyseal disk was perforated, and only traces of cartilage were left.

IV. Strain New Buffalo (with a moderately slow rate of ageing). Four groups of animals 10, 12, 14 to 16, and 19 to 24 months old were examined.

In 10-month-old males, the epiphyseal cartilage cells were more numerous and better preserved than in breeding females. In the latter, almost the entire cartilage had been converted into calcified, amorphous material, and in one animal a perforation had already occurred. Conditions in the growth zone of the virgin female were intermediate between those of the males and the least advanced breeding females.

In the 12-month-old virgin and breeding females, the histological structure of the cartilage was similar to that seen at the age of 10 months. In the males, however, the age changes had made further progress so that the sex differences were now less conspicuous than at the earlier age. Still, there were no perforations in the epiphyseal disk in males, whereas advanced resorption was found in two of three breeding females. Very little change took place in either sex during the next few months, but at 14 months of age, the histological findings were similar in breeding and virgin females and males.

In contrast to the previous stage, resorption of the epiphyseal plate had advanced markedly in all males 19 months of age and older; however, epiphyseo-diaphyseal union had not made further progress in the corresponding breeding females.

V. Strain A (moderately rapid rate of ageing, marked bone-forming tendency). Six groups of animals 6, 7, 9 to 11, 12, 13, and 16 to 20 months old were examined.

At 6 months of age, the growth zones were composed of large amounts of inactive cartilage in both the male and female. In the male, regressive changes in the cartilage were not very marked; but considerable hyalinization and large areas of degeneration were noted in the female.

Seven-month-old virgin females still failed to show plugs of degenerated cartilage, whereas such areas were observed in both the males and breeding females. In the latter, however, they were more numerous and of larger size than in the former.

In 9- to 11-month-old mice, the number of cartilage cells had further decreased in the breeding female, whereas in the male and virgin female the amount of cartilage had remained unchanged as compared with the earlier age. Regressive changes had made progress in all groups. This was true particularly in the virgin females whose epiphyseal disks resembled now more closely those of the breeding females than before. However, in the breeding female the ageing of the cartilage was further advanced than in the virgin females and males.

During the next 2 and 3 months, at 12 to 13 months of age, the breeding females and males showed comparatively little alteration of the epiphyseal plates.

In the 14-month-old mice, ageing of the epiphyseal zone proceeded more slowly in the virgin female than in either the males or breeding females. The males showed still more and better preserved cartilage than the breeding females; in the latter, many large plugs of disintegrated cartilage had replaced most of the epiphyseal disk; such cartilage as remained, had undergone marked hyalinization; one of the breeders showed beginning perforations of the growth zones. But on the whole, perforations in this strain were rare even in very old mice, irrespective of sex and breeding activity.

From the age of 16 months on, there was scarcely any difference in the structure of the epiphyseal plates of virgin or breeding females and males. In other words, the age changes in the males and virgin females were now similar to those of the breeding females and reached a stage, where no further progress was made. Even a group of three males, 22 months old, failed to show any progressive changes as compared with the conditions in the preceding stage.

VI. Strain C₃H (rapidly ageing with a marked tendency to bone-formation). Five groups of animals 4, 8 to 9, 13, 15, and 19 months and older were studied.

Up to the age of 9 months, the epiphyseal plates of the males (fig. 4) and virgin females (fig. 6) were much better preserved, and they showed fewer and smaller areas of degeneration than those of the breeding females (fig. 5).

At the beginning of the second year of life, these differences became less sharp. The amount of cartilage present and its state of regression were similar in all three groups of mice. After 15 months of age, the

remaining cartilage was gradually ossified. Perforations were seen only in one breeding female and in three males among the ten mice that had lived beyond the age of 1 year.

VII. Strain D (rapidly ageing). Four groups of animals 6 to 7, 8 to 9, 12, 14, and 19 to 20 months old were examined.

This strain ages so rapidly that as early as the age of 6 months, there was scarcely any difference between males and breeding and virgin females as to the amount of cartilage present and its state of preservation. However, in breeding females the growth zones had already been broken through, whereas in the males and virgin females there was at most merely a suggestion of perforations.

In the animals 8 to 9 months old, the age changes had made only very little progress in the virgin and breeding females as compared with those in the earlier stage. In the males, on the other hand, the epiphyseal cartilage had begun to age more rapidly. This was indicated by an increased ossification and by the progress of resorptive processes leading to perforations of the epiphyseal plate. Thus, conditions in males and females resembled each other more closely than before.

During the second year of life, scarcely any difference was noticeable in the growth zones of males, and virgin and breeding females. There was little cartilage present, and it was in an advanced stage of regression. In the one male and the one virgin female living more than 1½ years no further age changes had taken place.

B. Conditions in the joints

With advancing age, the articular cartilage underwent changes of varying degree. As in previous investigations, the following gradations of the joint lesions were made: Grade I showing slight proliferation and hypertrophy of the cartilage, grade II characterized by a moderate degree of both regressive and growth processes, and grade III showing marked degeneration and hyperplasia of the cartilage comparable to osteoarthritis.

The findings in the various strains of mice are shown in tables 2 and 3.

Table 2 gives the incidence of joint lesions in each strain and their distribution in males (m) and virgin (v) and breeding (b) females. In each strain, the joints of virgin females were less affected than those of males or breeding females. Virgin females revealed the highest percentage of normal joints (col. 5) and the lowest incidence of the more severe lesions (col. 7, 8). In males and breeding females, there was little difference in the incidence of grade II and III changes. Such differences as did exist, might have been due to variations in the age of

the mice: In strain CBA, for instance, grade II and III changes in males amounted to 86% (col. 7, 8), whereas in females they were only 67%. However, as seen from table 1, six of seven or 86% of the males were older than 1 year, whereas of three breeding females only two or 67% were of corresponding age.

TABLE 1

Showing the distribution of the animals according to strain, age and sex.

AGE GROUP	C57 22 AN. m v b	O.B. 15 AN. m v b	CBA 12 AN. m v b	N.B. 24 AN. m v b	A 37 AN. m v b	C ₃ H ¹ 20 AN. m v b	D 17 AN. m v b	TOTAL
A								
6-12 mos.	4 1 3	1 1 0	1 0 1	2 1 3	3 4 7	4 2 4	3 3 4	52
B								
12-18 mos.	3 3 2	3 4 3	1 1 1	4 2 6	7 2 6	4 2 2	2 2 1	61
C								
18-30 mos.	1 3 2	3 0 0	5 1 1	4 0 2	6 1 1	2 0 0	1 1 0	34
Total	8 7 7	7 5 5	7 2 3	10 3 11	16 7 14	10 4 6	6 6 5	147

m—Males: 64 animals. v—Virgins: 34 animals. b—Breeding females: 49 animals.

¹ Age group A of this strain contained one set of animals 4 months of age (1 male, 1 virgin and 1 breeding female).

Table 2 also gives some indication as to the susceptibility to joint lesions of the various strains: Strain Old Buffalo was resistant, since the percentage of normal joints and of grade I lesions was high in males as well as in virgin and breeding females (col. 5, 6). Likewise in strain C57, the incidence of the normal joints and of grade I changes was higher than that of the more severe alterations of grades II and III. Strain CBA was actually more resistant than would appear at first sight. No normal joints were found in the males; but this is probably due to the fact that the males used were very old (table 1). Conversely strains C₃H and D were more prone to develop articular changes than appears from the table. According to table 1, one-half of these mice was under 1 year of age, and in strain C₃H there was included one set of very young animals of only 4 months of age.

INCIDENCE OF ARTICULAR CHANGES IN THE THREE AGE GROUPS

Table 3 shows the incidence and severity of joint changes in males (m) and virgin (v) and breeding (b) females, and their distribution in the three age groups without regard to the strain. As seen from table

TABLE 2

Showing the incidence of joint lesions in each strain and their distribution in males, and virgin and breeding females.

STRAIN	NO. OF ANIMAL	SEX	DISTRIBUTION IN PERCENT	CHANGES IN PERCENT GRADE			
				0	I	II	III
C57	22	m	36.4	12	63	25	0
		v	31.8	43	43	0	14
		b	31.8	29	28	29	14
O.B.	15	m	46.7	42	29	0	29
		v	33.3	80	20	0	0
		b	20.0	67	33	0	0
CBA	12	m	58.3	0	14	28	58
		v	16.7	100	0	0	0
		b	25.0	33	0	0	67
N.B.	24	m	41.7	20	30	30	20
		v	12.5	34	33	33	0
		b	45.8	18	36	46	0
A	37	m	43.2	19	31	38	12
		v	18.9	57	29	0	14
		b	37.9	28	14	36	22
C ₃ H	20	m	50.0	30	20	10	40
		v	20.0	75	25	0	0
		b	30.0	17	33	17	33
D	17	m	35.3	17	50	33	0
		v	35.3	33	50	0	17
		b	29.4	20	40	40	0

TABLE 3

Showing the incidence and severity of joint changes in males and virgin and breeding females and their distribution in the three age groups.

	NO. OF ANIMAL	AGE GROUP	PERCENT OF TOTAL	CHANGES IN PERCENT GRADE			
				0	I	II	III
Males	64	A	28.0	28	39	28	5
		B	37.5	17	29	25	29
		C	34.5	18	32	23	27
Virgins	34	A	35.4	75	8	8	9
		B	47.0	44	56	0	0
		C	17.6	50	17	0	33
Breeding females	49	A	44.9	18	36	32	14
		B	42.9	29	19	33	19
		C	12.2	66	17	17	0

1, age group A comprises animals 6 to 12 months old, group B those 12 to 18 months of age, and group C those over 18 months of age.

In age group A, virgin females had more normal joints (75%) than either males (28%) or breeding females (18%). Severe lesions (col. 7, 8) were somewhat more frequent in the breeding females (46%) than in the males (33%); they were distinctly rarer in the virgin females (17%).

In age group B, virgin females again showed the highest number of normal joints (44%) as compared with 29% in breeding females and 17% in males. The incidence of grade II and III changes was about the same in males (54%) and breeding females (52%). However, in the male, there was a marked tendency to grade III lesions (29%); in breeding females, their incidence was 19% only. In virgin females on the other hand, there were no lesions of either grade II or III.

In age group C, the breeding females presented a large number of negative cases (66%), whereas normal joints were less numerous in virgin females (50%) and even fewer in males (18%). The incidence of severe changes (col. 7, 8) was highest in males (50%); it was lower in virgin (33%) and lowest in breeding females (17%).

Males had the lowest incidence of joint changes in age group A, normal joints and grade I alterations amounting to 67%, grade II and grade III lesions to 33% (col. 7); in age groups B and C, conditions in the joints were about equal: In group B, there were 46% normal joints and grade I changes and 54% lesions of grades II and III; the corresponding figures in age group C were both 50%. This means that articular changes became conspicuous in middle life, but did not increase in frequency or severity in old age.

Virgin females showed a low incidence of joint changes in all age groups: In age group A, the negative and grade I cases amounted to 83%, in group B to 100% and in age group C to 67%. The highest percentage of severe lesions (33%) was found in age group C. This would indicate that the factors responsible for the articular changes acted more slowly in the virgin female than in the male and became effective only in old age.

Breeding females revealed a 54% incidence of normal joints and grade I changes in age group A as compared with 48% in group B and 83% in age group C. But, there were fewer negative and grade I cases than in virgin females or males of corresponding age, this in spite of the fact that more breeders (44.9) were in the younger age group than either virgin females (35.4%) or males (28%). Severe lesions on the other hand, had an incidence of 46% in age group A and of 52% in age group B, whereas their incidence was only 17% in age group C (col. 7, 8).

COMMENT

The present investigation confirms and supplements our previous findings as to sex differences in skeletal ageing of mice (Silberberg and Silberberg, '41 a). The results obtained are also in agreement with gross observations on skeletal development in humans (Pryor, '23; Greulich, '42), rats (Spark and Dawson, '28) and chickens (Latimer, '27). These investigators found skeletal maturation accelerated in the females as compared with the males.

During the first year of life, the epiphyseal cartilage of breeding female mice showed more pronounced and further advanced regressive changes than that of males of the same age. Subsequently, ageing proceeded more rapidly in males than in females; thus between the age of 12 and 15 months, in most strains examined, the males reached an advanced degree of epiphyseo-diaphyseal union. In the female on the other hand, the age changes remained at this time of life stationary or made only slight progress.

But there were in addition some differences noticeable among the females, the cartilage of virgin females in general being better preserved than that of breeders. This was conspicuous already in a series of 4 months old mice of strain C₃H. The cartilage of the breeding female had undergone more widespread and more extensive destruction than that of the virgin. Moreover in the breeder, marked resorption of degenerated cartilage suggested an impending perforation, a rather unusual occurrence in this strain. This very young breeder had probably one but certainly not more than two pregnancies. Breeding, thus, apparently exerts a potent ageing effect on the cartilage, and correspondingly the cartilage of very young mice may be very sensitive to the modifying action of pregnancy. This response is somewhat analogous to findings in virgin females and male mice treated with hormones (Silberberg and Silberberg, '43): The cartilage of young animals was found to react more intensely to hormonal stimulation than that of older ones. A single pregnancy occurring in early life may thus exert a more pronounced ageing effect on the cartilage than several pregnancies occurring later in life. The rapid degeneration of the epiphyseal cartilage during pregnancy may be due primarily to the influence of estrogen, but anterior hypophyseal hormones may likewise play a part. The role of estrogen may also be indicated by the relatively slow progress of epiphyseo-diaphyseal union in breeders as compared with that of males and virgin females. In growing mice, estrogen besides accelerating the ageing of the cartilage inhibits resorption and thus delays the progress of epiphyseo-diaphyseal union. In males on

the other hand, the inhibition by estrogen is lacking, and the inhibition of resorption exerted by androgen is less marked: Thus, epiphyseo-diaphyseal union may proceed with greater intensity toward the limit set by the genetic constitution of the strain. Conditions may be similar in virgin females, who are likewise exposed to lesser amounts of estrogenic hormones than breeders and, therefore, may show wider perforations and a more advanced degree of epiphyseo-diaphyseal union than breeders. However, even in the breeder, the effect of hormonal stimulation may interact with the genetic determination of age changes. Thus, in strains C57 and CBA old breeders may eventually develop epiphyseo-diaphyseal union; in strains A and C₃H on the other hand, the marked bone formation (genetic factor) and the inhibition of resorption (hormonal factor) cooperate in making perforations of the epiphyseal disk a rare occurrence.

As compared with males, the progress of skeletal ageing of virgin females varied: In the slowly ageing strains C57 and CBA, the early age changes in males were retarded as compared with those of the virgin females; on the other hand, in the more rapidly ageing strains A, C₃H and D, these differences were less accentuated and disappeared at an earlier age than in the slowly ageing strains.

As to the joint changes, a certain trend seems to be discernible despite the fact that the number of animals in the individual groups is limited. It is planned to extend these investigations at a future date. Our present observations may be summarized as follows: Virgin females of all strains and ages were distinctly less affected than corresponding males or breeding females; but even virgin females did develop severe lesions in old age. Therefore, in virgin females the factors responsible for these changes probably develop only late in life or they require more time to accumulate in sufficient strength to cause these lesions. In males, on the other hand, the joint changes did not increase in severity or frequency in old age, while in breeding females the articular lesions were even slightly more numerous than in males and they were somewhat more severe during the first year of life: During the first half of the second year of life, males and female breeders were about equally affected; but at later periods, the incidence and severity of articular changes dropped sharply in the breeding female.

Thus it appears that (1) the factors leading to joint lesions become active earlier in the life of breeding females than in either males or virgin females; (2) that these factors do not increase in potency in old age. The smaller number of joint changes in old breeding females may be attributable to the fact that among the breeders only very resistant

individuals reach the higher age groups (Loeb, '19; Little, Murray and Cloudman, '39). The low susceptibility of such animals to articular changes may then be only another symptom of their general resistance to disease.

Only tentative explanations can be ventured as to the nature of the factors causing the articular lesions: Their late appearance in virgins might indicate that they are partly due to old age changes in the cartilage. In males, their aggravation during the first half of the second year of life and the decline of the sexual function at this time may be a coincidence, but there is a possibility that it may be connected with the imbalance of sex life characteristic of this period. Administration of anterior hypophyseal hormone or transplantation of anterior hypophyseal glands increase the incidence and severity of such joint lesions and hasten their onset (Silberberg and Silberberg, '41 b). The excess of anterior hypophyseal hormones released after cessation of the testicular function might play a part either in initiating the joint changes or in intensifying abnormal conditions in cartilage that begins to age. Fundamentally, conditions might be similar in breeding females, even though they develop articular lesions at an earlier age than males. In breeding females, the activity of anterior hypophyseal hormone or of anterior hypophysis-like hormones is greatly enhanced during pregnancy. An increased output of anterior hypophyseal or chorionic hormones might affect the articular cartilage and promote the age changes in it. Estrogen has probably no active role in the causation of the joint lesions, since it produces sclerosis and atrophy but no growth stimulation of the cartilage.

SUMMARY

In mice, breeding accelerates skeletal ageing: Onset and progress of the age changes in virgin females are delayed as compared with conditions in breeding females and males. In males, skeletal ageing takes at first a slower course than it does in females, but subsequently the age changes proceed more rapidly in males than in either the virgin or breeding females.

In virgin females, articular age changes are rarer and less severe than in either males or breeding females. Joint lesions appear earlier in breeding females and they are in a first stage more severe than in males. However, in old males, the joints may be more frequently and more severely affected than in breeding females.

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PLATE 1

EXPLANATION OF FIGURES

Sections through the epiphyseal disks of the upper tibiae of mice of strain Old Buffalo, 18 months of age. Magnification 93 $\times$.

- 1 Male: Advanced degree of epiphyseo-diaphyseal union with only traces of cartilage left.
- 2 Breeding female: Some inactive cartilage left; center of growth zone converted into a thin bony scar; no perforation of the epiphyseal disk.
- 3 Virgin female: Cartilage better preserved than in either male (fig. 1) or breeding female (fig. 2), but inactive and markedly calcified; no perforation of the growth zone.

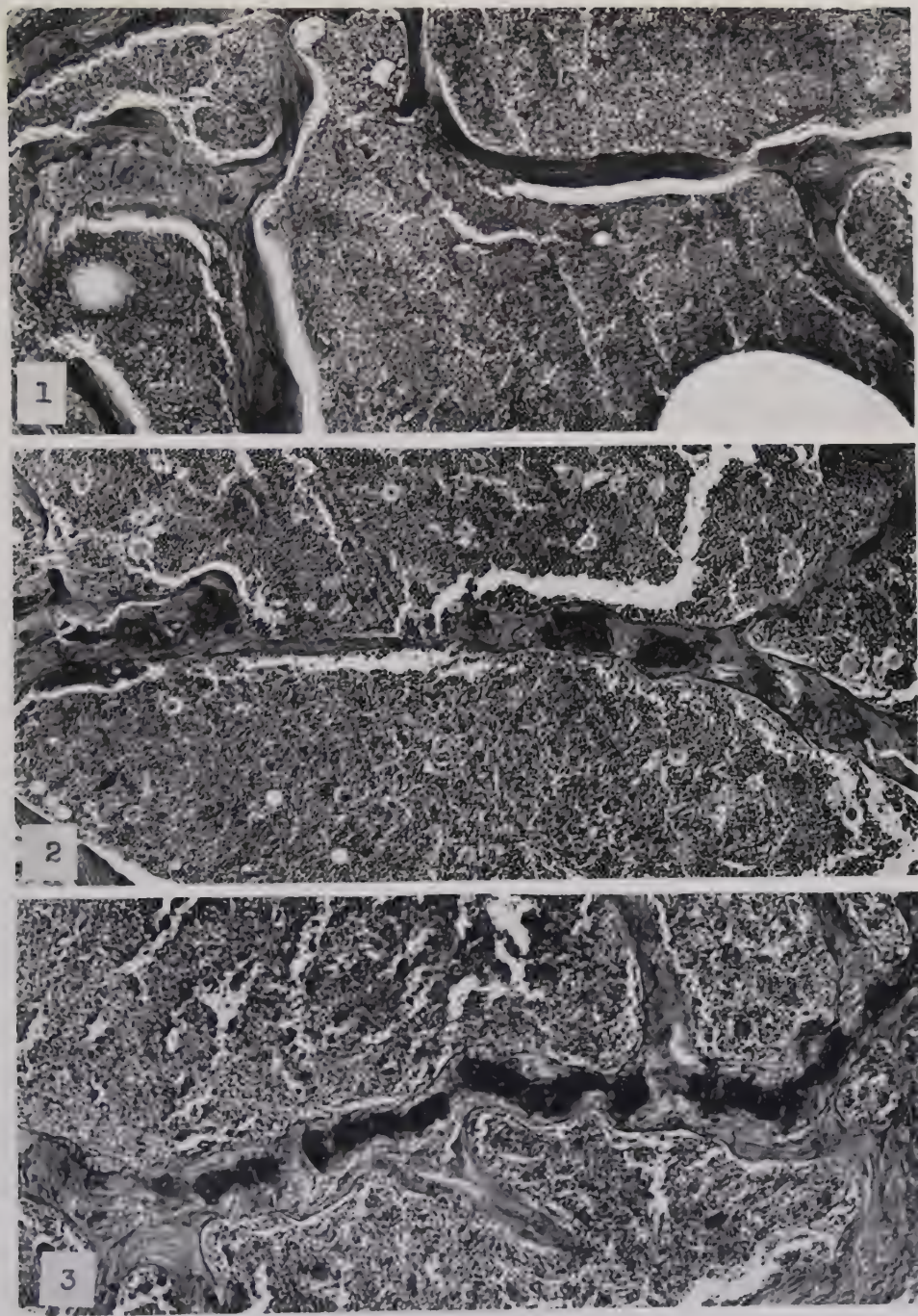


PLATE 2

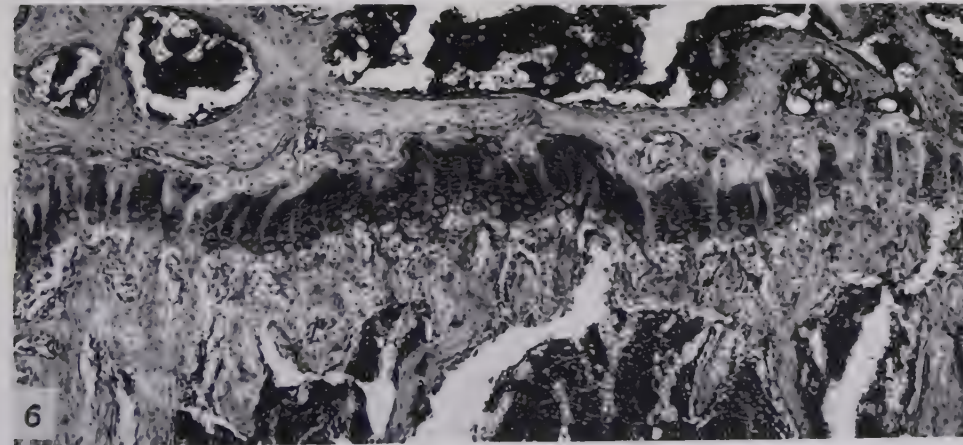
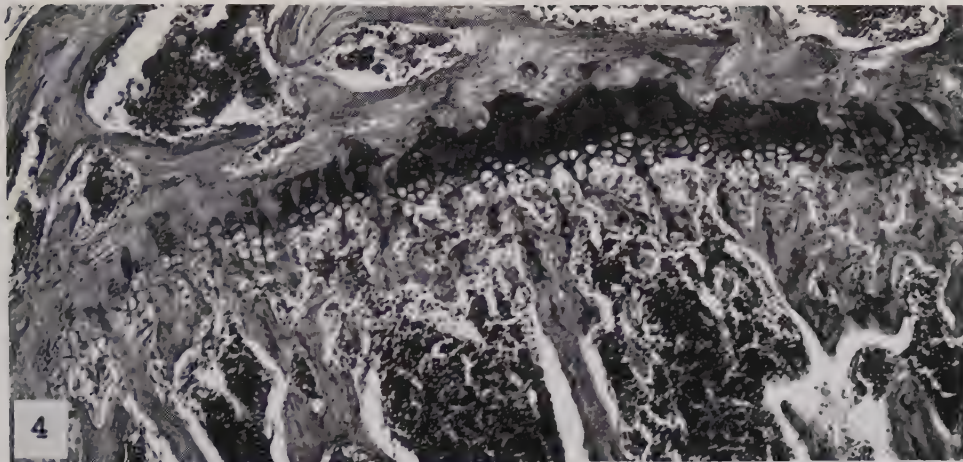
EXPLANATION OF FIGURES

Sections through the epiphyseal disks of the upper tibiae of mice of strain C₃H, 4 months of age. Magnification 93 X.

4 Male: Cartilage calcified, small hyaline wedges between the cartilage columns and small plugs of degenerated cartilage beginning to form.

5 Breeding female: Two plugs of degenerated cartilage in the growth zone.

6 Virgin female: Cartilage better preserved showing some hyalinization of the ground substance, but no "plugs".



THE HISTOGENESIS OF THE ARGENTAFFIN CELLS IN THE STOMACH AND DUODENUM OF THE RAT

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TWO PLATES (SIX FIGURES)

The demonstration of a relatively high incidence of argentaffin cells in the gastric mucosa of the adult rat (Dawson, '44), by an adaptation of the Bodian protargol method (Dawson and Barnett, '44), prompted this study of the histogenesis of these specialized cells of the gastrointestinal tract. Good data are available on the number and distribution of argentaffin cells for the entire intestinal canal of the adult rat (Münch, '39) but no studies on their histogenesis have been found. An excellent account of the early histogenesis of the more readily demonstrated constituents of the epithelium of the stomach and small intestine by Kammeraad ('42) greatly facilitated this study.

The information on the time of appearance and rate of increase in the number of argentaffin cells in the digestive tract of mammals is scattered and incomplete. Parat ('24 a and b) reported them in the intestine of human embryos between the fourth and fifth months of intrauterine life while others have indicated their presence at the end of the third month (Cordier, '26; Friedman, '34). Parat ('24a) also states that it is almost impossible to detect these cells in embryonic sheep, cats, horses, dogs and guinea pigs until near the end of the period of gestation. They are first seen, according to him, in embryos of the fiftieth to fifty-seventh day and none were present at the fortieth day. However, Tehver ('30) records the presence of argentaffin cells somewhat earlier in several mammals: calf embryo, 7.5 cm. long, ca. 8 weeks, in the abomasum and intestinal canal; sheep embryo, 11.5 cm. long, ca. 10 to 11 weeks, in intestine only; pig embryo, 14 cm. long, ca. 2½ months, few in stomach, numerous in intestine; dog embryo, 8 cm. long, ca. 6 weeks, distributed in both stomach and intestine. Schumann ('39) finds that they are absent in guinea pig embryos 35 mm. long (crown-rump) but present in the intestine of 50 mm. embryos in considerable numbers.

¹This study was carried out under the direction of Prof. Alden B. Dawson and was presented as part of a senior thesis in partial fulfillment of the requirements for the S. B. degree, with honors in Biology, Radcliffe College, 1944.

He counted totals of 272, 345 and 289 cells respectively in the first 3 cm. of the upper duodenum of three different embryos. The more significant relationship between the first appearance of argentaffin cells and the level of histogenesis of the epithelium of the stomach and intestine has in most instances received but cursory attention.

MATERIALS AND METHODS

Embryos used in this study were removed from the uterus at 15, 17 and 19 days after mating. They were fixed *in toto* after slitting the abdominal wall and the gastrointestinal tract was subsequently dissected free. The postnatal stages studied included the newborn rat and rats aged 5, 10, 15, 25, 35, 60, 90 days, and the adult. Particular attention was paid to the fundic and pyloric regions of the stomach and the upper duodenum. The cardiac region was omitted from consideration.

All tissues were fixed for 48 hours in Bodian's formol-acetic acid-alcohol mixture, dehydrated, cleared in cedar oil, embedded in paraffin and sectioned at 7 micra. The treatment with protargol (24 hours) and subsequent reduction were repeated once. Toning with gold chloride was omitted. In the final preparations the argentaffin cells were stained brown to deep black while the rest of the tissue provided a golden-yellow background.

HISTOGENESIS

In the adult rat, the epithelium of the stomach consists of two types, esophageal or stratified squamous and gastric proper or glandular. Since argentaffin cells were not found at any time in the stratified squamous epithelium, no reference to the histogenesis of this region need be made. The gastric epithelium is subdivided into cardiac, fundic and pyloric regions. This description of the histogenesis of the glandular portion of the stomach and of the intestine is based largely on the work of Kammeraad ('42).

Early in development the epithelium of the glandular stomach becomes stratified and is relatively thick. The first evidence of histodifferentiation is the appearance of intra-epithelial vacuoles in the 15½-day embryo. The vacuoles eventually rupture onto the free surface and represent precursors of the gastric pits. During the nineteenth day of intrauterine life the stratified epithelium is transformed into a simple epithelium and upgrowths of mesoderm produce villus-like projections which are separated by the gastric pits.

The first stage in the development of gastric glands appears in the newborn animal when small epithelial evaginations invade the under-

lying mesenchyme. At the end of the first day, short gastric (fundic) glands, with chief and parietal cells, are present. In the succeeding days the glands are extended until, in the 25-day-old animal, the pattern is very similar to that of the adult, with chief cells located mostly in the basal half of the gland. During the first 10 days of postnatal development the chief cells contain few pepsinogen granules and it is only in the 25-day animal that the full complement of granules is present. Thereafter there is a gradual increase in the length of the glands and in the numbers of chief and parietal cells.

The presence in the 17-day embryo of irregular epithelial protrusions on the free surface of the stratified epithelium of the duodenum is the first evidence of histological differentiation in the small intestine. In the 17½-day embryo the primitive villi possess cores of mesenchyme and intraepithelial vacuoles are prominent. By the nineteenth day the villi of the duodenum are short, stout but well defined and goblet cells make their first appearance on the twentieth day. In the newborn animal the crypts of Lieberkühn are represented by small evaginations of the epithelium between the bases of the villi. At this time the villi themselves are no longer broad and thick but are greatly elongated.

ARGENTAFFIN CELLS OF THE STOMACH

Argentaffin cells first appear in the stomach of the newborn rat but are limited at this age to the fundic portion. Here only occasional cells are seen, usually in the epithelium of the developing fundic glands. They are frequently rounded with granules (brown to black) distributed loosely through the cytoplasm. A few cells are triangular in outline with the granules aggregated basally. Rarely a cell may be found in the epithelium of the base of the gastric pits and none appear in the superficial epithelium.

In the stomach of the 5-day-old rat the argentaffin cells are only slightly increased in number although the gastric tubules have increased in length, and in the number of chief and parietal cells that they possess. Only one or two argentaffin cells may be seen in one high-power field and they are confined to the bases of the glands. They are more characteristic in appearance than those of the newborn animal and are clearly outlined by their granulation. Some can be found with their granular processes extending between the neighboring cells. Only an occasional argentaffin cell appears in the pyloric region at this age. By the tenth day the number of argentaffin cells in the fundic region is about double that of the fifth day but in the pyloric region the cells are still few and scattered.

There is a small rise in the number of argentaffin cells in the fundus of the 15-day-old rat over the number present on the tenth day and the pyloric glands contain only a few more cells. In the fundus of the 20-day rat the argentaffin cells are well scattered throughout the lower half of the gastric glands, paralleling rather closely the distribution of the chief cells (fig. 1). The argentaffin cells are not so heavily granulated as in later stages. They lie between and peripheral to the chief cells and there is a greater number of granular, protoplasmic extensions between the cells of the tubular epithelium of the glands. In the pyloric glands only one-half the number of cells seen in the fundus are present.

On the twenty-fifth day the fundus shows a 50% increase in the number of argentaffin cells over that of the 20-day fundus. This is the end of an active stage in the differentiation of the stomach since at this time the gastric glands assume their typical appearance and the chief cells become fully granulated. The number of argentaffin cells is about one-quarter of that found in the adult animal. The number of argentaffin cells in the pylorus at this age is still slightly less than that of the fundus of the 20-day-old rat and this represents almost a maximum concentration of these cells for this area. After this time there is but an increase in number proportional to the growth of the pyloric region and the concentration of cells appears to remain rather uniform and comparable to that in the adult.

The number of argentaffin cells in the fundus of the 35-day-old rat falls short of the adult number by about one-half. Otherwise the cells are typical in form and distribution. At 60 days the fundus contains about 75% of the number of cells present in the mature rat (figs. 2 and 3). Even at 90 days the fundus still does not have the adult amount of argentaffin cells. However, the difference is not very great. The full complement is attained only at maturity. No observations have been made on the influence of aging or sexual activity on the relative number of cells present in the adult animals.

ARGENTAFFIN CELLS OF THE DUODENUM

Argentaffin cells are first found in the duodenal epithelium, close to the pylorus. Occasional cells may be present as early as the fifteenth day of gestation. There are no villi at this stage and the epithelium is still stratified. The sparsely scattered cells are usually rounded with scanty, uniformly distributed granules and are found at various levels in the stratified epithelium. In the upper duodenum of the 17-day embryo the argentaffin cells are slightly increased in number. They tend to be located away from the lumen and the majority of the cells appear

as elongated elements wedged between the basal, columnar cells of the stratified epithelium. Occasional rounded cells may be seen in the more superficial strata.

At the nineteenth day the villi are well defined and growing rapidly and the epithelium has been almost completely transformed from a stratified into a simple columnar type. The argentaffin cells are more numerous and some closely resemble, both in form and position in the epithelium, the argentaffin cells of the adult intestine. They are long and thin, lie between the columnar cells, and frequently extend to the lumen of the intestine. In other locations, especially in the epithelium between the bases of the villi, round cells may still be seen and transitional stages between these two types may be found. The argentaffin cells occur unevenly, several in one group of villi and sometimes none in an entire cross section of the duodenum. Random counts made near the pylorus may vary from none to 15 cells per cross section.

In the newborn rat the argentaffin cells of the duodenum stand out sharply (fig. 4). They are present in relatively large numbers, proportionately more in the epithelium of the villi than at any other time in the life of the rat. Their distribution, as usual, is uneven, some villi possessing five or six of them while others have none. They appear to be distributed widely and at random in the epithelium of villi and are rarely seen in the developing crypts of Lieberkühn.

The argentaffin cells are rounded in the crypts and at the bases of the villi, but have a tendency to become compressed into a more flask-like form further up on the villi. However, many cells are less elongated than those typical of the adult and they do not always extend to the lumen. The granulation of many cells is dense and often obscures the nucleus and fills the entire cell. In others the granulation is limited to a basal position and occasional cells are slender with a scanty, but diffuse, brown granulation.

At 5 days of age the argentaffin cells of the duodenum are strikingly less numerous (about one-half) than in the newborn animal, although as many as six are not uncommon in many high-power fields. They are, however, more uniformly distributed among the villi and crypts. In the villi the cells characteristically reach the intestinal lumen and are larger and more heavily granulated than those seen in the stomach at this age. They are usually stout basally, with a slender neck extending to the free surface. Some appear to be about twice as large as the neighboring columnar cells. This description applies only to the portion of the duodenum immediately adjacent to the pylorus. As the sections progress caudally there is a fairly sharp decline in the number

of cells. There is also a rather steep antero-posterior gradient in the histogenesis of the small intestine, and in the adult, as Münch ('39) has pointed out, the concentration of argentaffin cells is high only in the first few centimeters of the duodenum and the number steadily decreases in the jejunum and ileum. The glands of Brunner also possess scattered argentaffin cells.

By the tenth day of postnatal life there is a moderate increase (about 30%) in argentaffin cells over those of the 5-day stage. They are found more often in the crypts than in the villi (fig. 5). Through the fifteenth and twentieth days the number of argentaffin cells increases slowly (fig. 6). Some single villi show as many as eight cells in a single cross section of the duodenum while others possess very few. There is an increased tendency for the greater proportion of the cells to be grouped in the lower portions of the villi and in the crypts. In the submucosa the argentaffin cells of the glands of Brunner do not appear to share in the general increase in numbers seen in the duodenal mucosa after the fifth day and they become increasingly rare with age. Furthermore, they are very inconspicuous even in the adult and found chiefly in the immediate vicinity of the pylorus.

By the twenty-fifth day both in number and distribution the argentaffin cells are comparable to those of the adult and no further change in the general pattern can be ascertained in later stages by simple inspection. Detailed counts have not been made.

DISCUSSION

It is interesting to note the rather close correlation between the active initiation of histogenesis in the stomach and duodenum and the first appearance of the argentaffin cells. They acquire a specific granulation just previous to the appearance of villi (fifteenth to seventeenth day of embryonal life) and at about the time of appearance of the gastric glands in the stomach (newborn). These cells are apparently of endodermal origin but the impregnation method used does not selectively demonstrate the cells until they are granulated. In the fundic portion of the stomach the number of cells increases gradually and the full complement of cells is not acquired until full growth is attained. In the pyloric region, however, a more or less relatively stable population is reached by the twenty-fifth day of postnatal life. In this respect the pylorus behaves more like a portion of the duodenum.

In general the duodenum exhibits a steady increase in the number of the cells with shifts in distribution from villi to crypts as the latter become fully differentiated and a relatively stable population is reached

at 25 days after birth with the numbers of cells increasing proportionately with the growth of the intestine. The only peculiarity in behavior is the attainment of a relatively high population at birth which subsequently recedes, to increase again gradually after the fifth day. This may be related in some way to pregnancy since Schumann ('39) has shown that in the female guinea pig the number of argentaffin cells in the upper duodenum is at least doubled toward the end of gestation and by the fourteenth day after parturition it has returned to normal.

SUMMARY

Argentaffin cells first appear in the fundic mucosa of the newborn rat at the time that the gastric glands make their appearance. In the fundic region the number of cells increases gradually until the rat is fully grown. In the pyloric region, where the number of cells is relatively few at all times, a comparatively static population is reached at 25 days after birth. No argentaffin cells appear at any time in the stratified squamous epithelium of the esophageal portion of the stomach.

In the duodenum argentaffin cells may be present as early as the fifteenth day of embryonal life but are characteristically present on the seventeenth day, the time of early differentiation of villi. These cells reach their highest relative number in the villi of the duodenum of the newborn animal. After a brief regression in number there is a relatively steady increase in number until the twenty-fifth day after birth, when the adult pattern of distribution in villi and crypts is attained. Argentaffin cells are present in the glands of Brunner at birth but the increase in number thereafter does not appear to keep pace with the growth of these glands.

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EXPLANATION OF PLATES

All figures are photomicrographs taken at a uniform magnification of 300 diameters. All tissues were prepared by the modified Bodian method without gold toning and cut at 7 micra. The argentaffin cells appear deep black in the illustrations.

PLATE 1

EXPLANATION OF FIGURES

- 1 Vertical section through the fundic mucosa of a 20-day-old rat showing the location, distribution and number of the argentaffin cells. The entire mucosa is shown.
- 2 Vertical section through a corresponding portion of the stomach of a 60-day-old rat showing the wider distribution and increased numbers of argentaffin cells at this age. Only the basal three-quarters of the mucosa is shown. There are no argentaffin cells above this region.
- 3 Vertical section through a corresponding region of the stomach of an adult rat showing an average population of argentaffin cells. Only the basal three-fifths of the mucosa is shown. There are a few scattered cells above this zone.

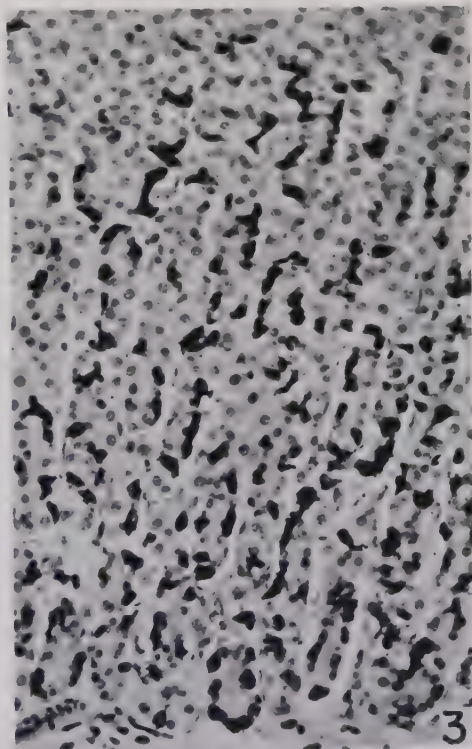
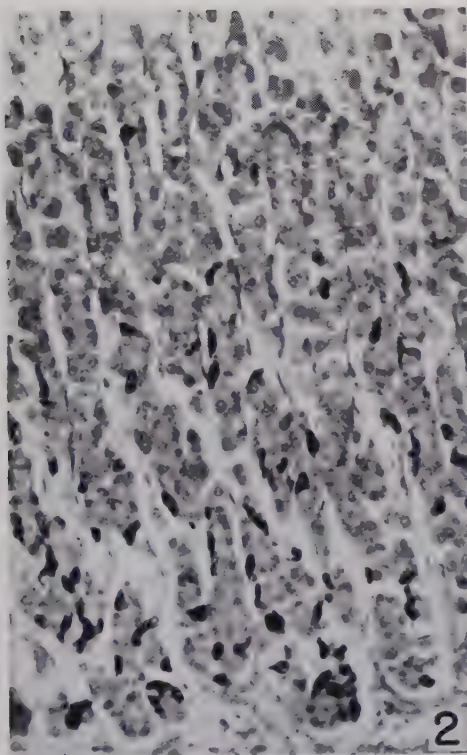
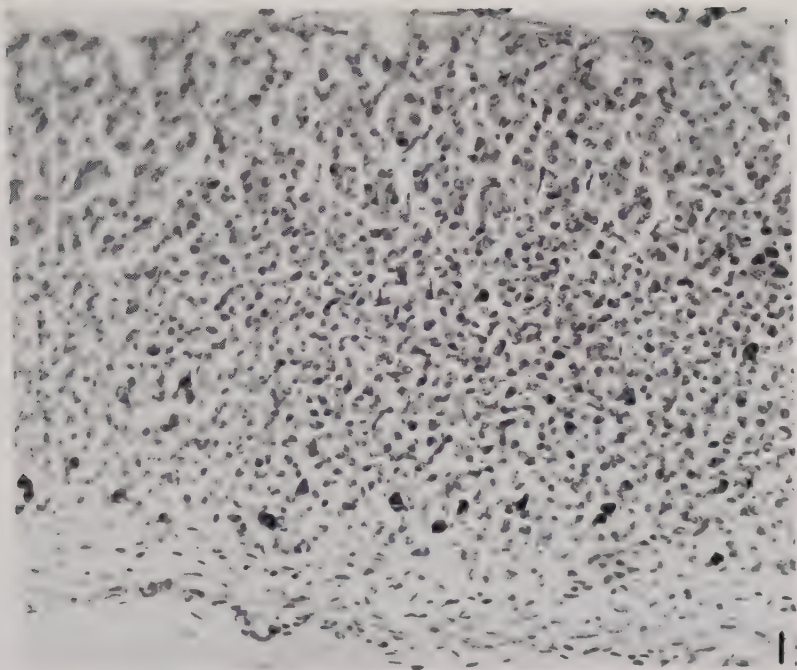


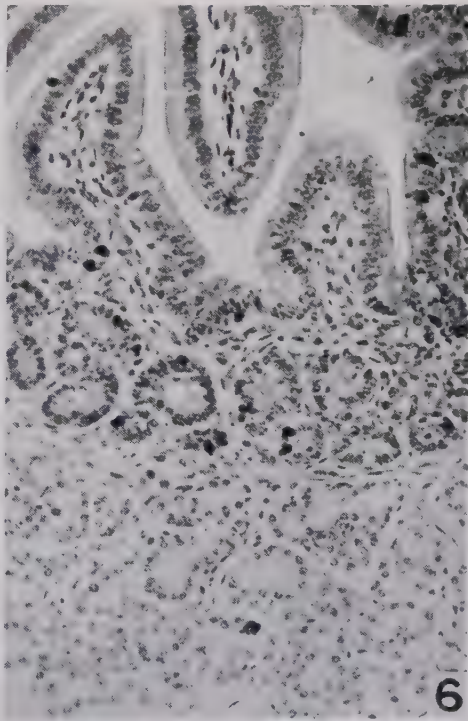
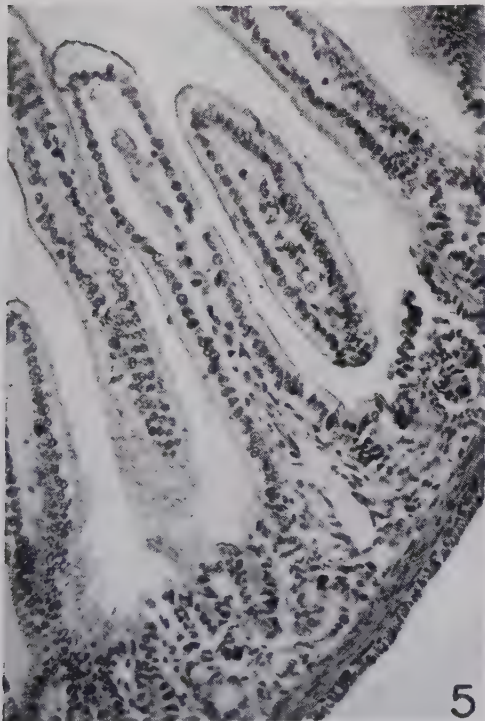
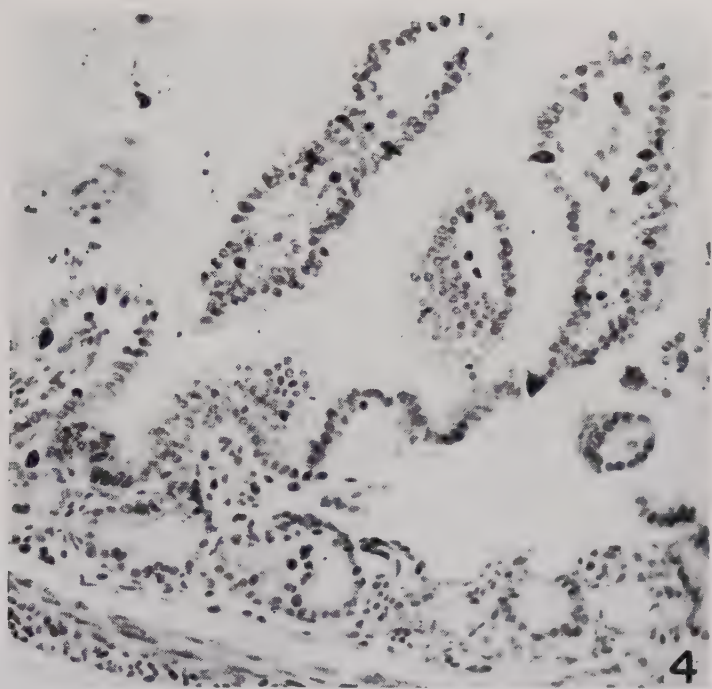
PLATE 2

EXPLANATION OF FIGURES

4 Portion of a transverse section of the upper duodenum of a newborn rat, showing the relatively high concentration of argentaffin cells in the epithelium of the villi.

5 Portion of a transverse section of the upper duodenum of a 10-day-old rat. The argentaffin cells are less numerous than in the newborn animal and appear more often in the crypts than in the villi.

6 Portion of a transverse section of the upper duodenum of a 20-day-old rat including an area of the glands of Brunner. The argentaffin cells appear to be about evenly distributed between the crypts and the villi. A single cell is present in a gland of Brunner.



DEVELOPMENT OF THE STERNUM IN SCREW TAIL MICE

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SEVEN TEXT FIGURES AND TWO PLATES (FOURTEEN FIGURES)

An understanding of morphogenesis may often be facilitated by modifying developmental processes in a determinate manner. Either by experimental methods or by studying the action of mutant genes, a means is provided to produce abnormal deviations in structure, and to learn from them the essential physiological and morphological steps through which an organism must progress if it is to be considered a normal individual.

MacDowell, Potter, Laanes and Ward ('42) have described a recessive mutation — screw tail, that modifies development in mice and produces a number of skeletal abnormalities. Some of the mutations modifying skeletal form in mice have relatively extreme effects (Gruneberg, '35; Dunn, Gluecksohn-Schoenheimer and Bryson, '41; Dunn and Gluecksohn-Schoenheimer, '42). In contrast, although the viability of screw tail mice is reduced, the phenotype is not grossly modified. Screw tail may therefore be compared with normal mice without raising the familiar objection that inferences drawn from highly teratological material are of doubtful significance in the interpretation of normal structure and function. In addition, a comparison of normal and screw tail mice is uncomplicated by the influence of residual genetic modifiers, since the mutation arose in the fiftieth generation of an inbred stock of CSH-Bagg albino mice.

Reviewed briefly, the effects of the screw tail gene as described by MacDowell et al. ('42) are as follows: At birth the tail is usually coiled into a corkscrew. As the mutant animal grows older, the coil straightens out until eventually the tail is distinguished primarily by a number of kinks. Sharp flexures may also appear in the lumbar or thoracic regions of adults. Instead of having six lumbar vertebrae, screw tail mice may have seven, the seventh representing the true first sacral, with the result that the pelvis is shifted caudally with reference to the vertebral column. Centra of individual lumbar and thoracic vertebrae

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are shortened. The sternum of screw tail mice is without segmentation, being a single short wide bone to which the second, and more rarely the third, costal cartilages may fail to attach. The teeth exhibit growth deficiencies most evident in the roots of the molars and the basal ends of the lower incisors. Malocclusion is typical and the mandible is malformed. Other abnormalities of the head include modification of the pattern of coronal and sagittal sutures and a change in direction of folding of the ear pinna, the latter expressed most frequently on the right side of the body. There is indication that new-born screw tail mice have a lower average weight than their normal sibs. Adult males and most adult females are sterile.

Since it would be impossible to deal adequately with all of the many effects of the screw tail gene in a single investigation, attention is confined in this study mainly to the development of the sternum, with emphasis on determining the principle events leading to the establishment of the normal segmented sternum and its unsegmented homologue in the screw tail mouse.

A widely prevalent but erroneous view of Ruge (1880) seeks to ascribe the genesis of the sternum to a proliferation of cartilage from the ends of the ribs. Neither Ruge's description nor the "in situ" theory of Whitehead and Waddell ('11) appears to be a correct interpretation of sternal origin. It is now generally agreed that Paterson's ('00) demonstration of a coracoidal derivation of the sternum in the rabbit, rat and human applies to vertebrates generally and that the amniote and anamniote sterna are in fact homologous. The anlagen of the sternum are to be found in the mesoderm of the primitive shoulder girdle (Hanson, '19; Gladstone and Wakeley, '32).

EMBRYOLOGICAL DEVELOPMENT OF THE STERNUM

Normal embryogeny

In the mouse as in all higher vertebrates, the sternum arises independently of the ribs through the caudad proliferation of two bands of mesoderm originating from the paired primordia of the presternum, closely associated at this period (12 days) with the omosternal pre-cartilages, clavicles and pectoral musculature. Examination of dissected specimens and sections reveals that the paired elements of the future sternum are at first widely separated by the pericardium, lying in the axillary region of the 12-day embryo in complete independence of the ribs with which they will later come into association. Movement of the paired omosternal elements and sternal apparatus to meet at the

sagittal plane is mediated by the growth of the clavicles to which the mesodermal rudiments of the omosternum and presternum are intimately attached (fig. 1). As the two sternal bands grow posteriorly in their lateral position they come, during the thirteenth day, to overlie and then to join with the ribs which are coincidentally growing out in

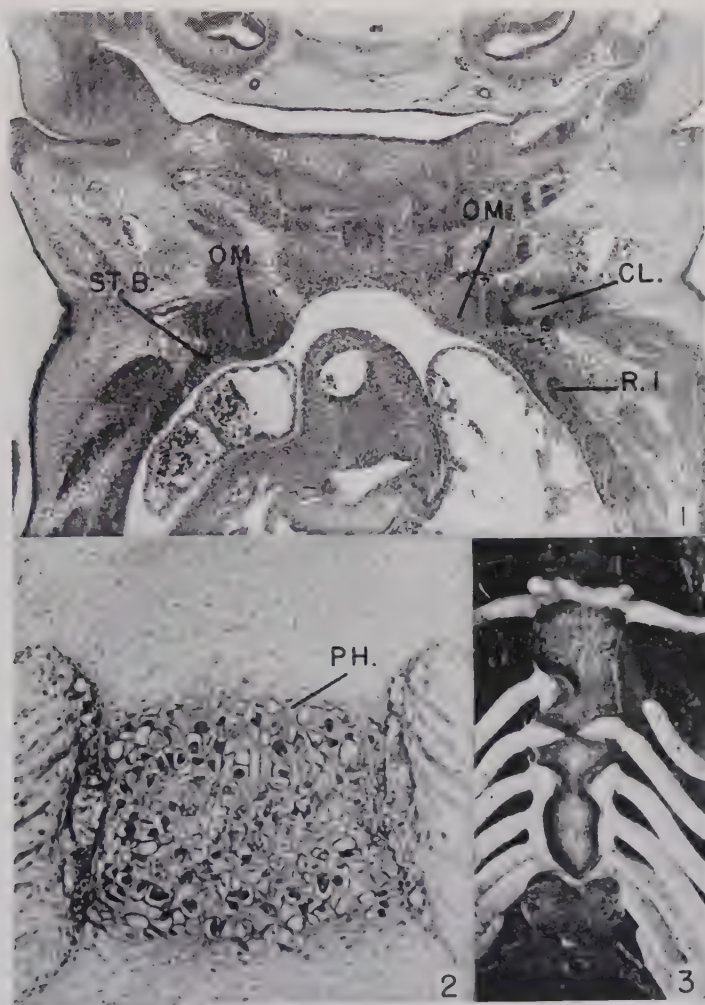


Fig. 1 Normal embryo. Age $13\frac{1}{2}$ days. Slightly asymmetrical frontal section. ST.B., sternal bands; O.M., omosternal cartilages; CL., clavicle; R.1., end of first rib. $40\times$.

Fig. 2 Normal embryo. Age 18 days. Frontal section of intercostal ossification center. Darkly stained matrical phosphatase (PH) bordering hypertrophied chondroblasts. Matrix continuity of immature cartilage cells is evident between costal cartilages and sternum. $100\times$.

Fig. 3 F_2 18-day screw tail embryo from Bagg albino screw tail $\times$ short ear. A suture is visible connecting sternal margins at the level of the third costal cartilages. $13\times$.

the myosepta of the thoracic vertebrae and around the lateral body wall in a plane at approximate right angles to the bands. Upon association the rib ends and sternal bands move together toward the median plane, bringing the paired sternal primordia into union anteriorly where the vault of the pericardium is least extensive, and resulting at the fourteenth day of embryonic life in the formation of a $\wedge$ with the apex directed anteriorly (fig. 5 a). Union of the sternal bands now proceeds anteroposteriorly until at the fifteenth day the paired anlagen of the sternum have united in the median plane. Except for a complete absence of segmentation into presternum (manubrium), mesosternum (sternebrae), and metasternum (xiphoid process), the 15-day cartilaginous sternum has assumed the principal anatomical outlines of the adult structure. Since at this time no sternebrae can be seen, the united sternal bands form a continuous bar of cartilage of bilateral origin (fig. 4 b).

Further changes are confined largely to the establishment and growth of ossification centers (figs. 4 b, d, f, h). Sternebral centers are invariably located intercostally and appear between the fifteenth and sixteenth day. The future centers of ossification are regionally demarcated at the sixteenth day through the hypertrophy of chondroblasts in definite regions corresponding in location to the sites of future bony elements of the sternum (figs. 4 b and 14). A dual origin of the centers is clearly evident in the region of the xiphoid process but is less apparent in the sternebrae and the manubrium because of the closer proximity of the hemisternebrae. At the seventeenth day ossification has begun. The sternum now begins to assume the appearance of a series of miniature bones arranged linearly, and interconnected by bands of cartilage at the sites of future articulations. Typically there are five articulations located invariably at the sternocostal junctions and separating six centers of bone formation, i.e. manubrium, four sternebrae, and the xiphoid process. Histologically the details of bone formation within each element follows the classical scheme; with periosteal ossification and a central core of endochondral osteogenic activity which progressively invades the surrounding region of eroded cartilage. Chondroblasts in various stages of hypertrophy and degeneration are arranged around the central core with smaller immature cartilage cells more superficially located.

Normal bone growth continues, interrupted only at the tip of the xiphoid which remains cartilaginous and in the region where ribs and sternum come in contact at the site of the future sternochondral joints. In embryos of 15 days or older, the matrix of sternum and costal carti-

lage is continuous with no periosteal barrier at the region of junction (figs. 2 and 14). At birth cartilagenous areas sparating the individual bony elements of the sternum are marked internally by two transverse bands, one directed medially from the tip of each rib, and characterized

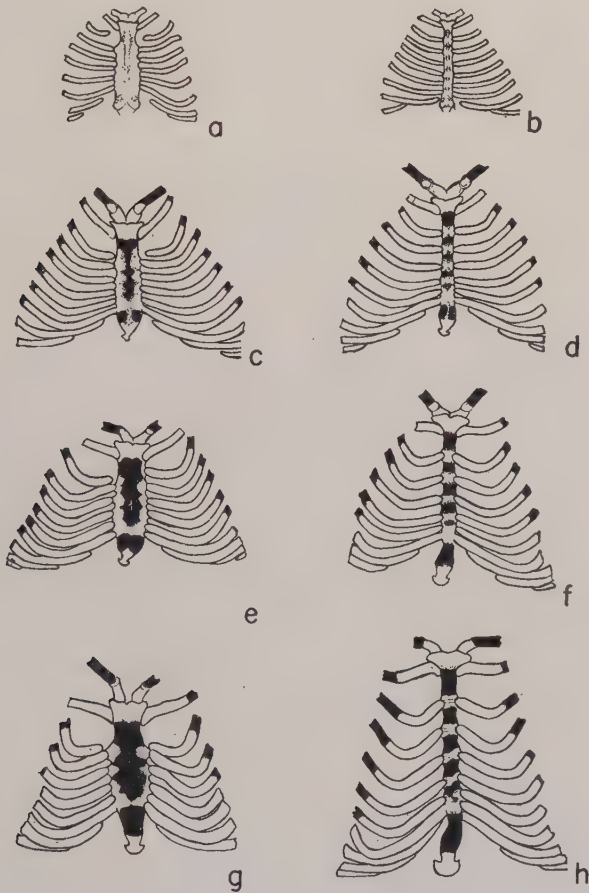


Fig. 4 Sternum and costal cartilages. Ossified areas in solid black. Camera lucida. $4\times$. (a) Screw tail embryo. Age 16 days. (b) Normal embryo. Age 16 days. (c) Screw tail embryo. Age $17\frac{1}{2}$ days. (d) Normal embryo. Age $17\frac{1}{2}$ days. (e) Screw tail embryo. Age $18\frac{1}{2}$ days. (f) Normal embryo. Age $18\frac{1}{2}$ days. (g) Screw tail animal. 1 day post partum. (h) Normal animal. 1 day post partum.

by a distinctly darker staining affinity of the matrix in sections stained with eosin azur. These dark regions presumably represent an early stage preparatory to the formation of an articular surface between sternebrae.

NATURE OF DIFFERENCES BETWEEN THE MUTANT AND NORMAL STERNUM

On the greater width of the mutant sternum

Reference to figure 4 will show that in comparison with the normal sternum, that of the screw tail mouse is wide, short and unsegmented. The interrelation of these three properties is not at first evident except that the shortness of the sternum is clearly a function of lack of segmentation, in that complete absence of the ten epiphyses normally present confines growth to periosteal bone deposit without the usual growth occurring at epiphyseal cartilage zones. The problem is then resolved into two major considerations: (1) Why is the sternum of the screw tail mouse wider than normal, and (2) How may one account for the failure of the mutant sternum to become subdivided into a number of separate bones? The descriptive evidence concerning these two problems will be considered in order.

At the thirteenth day the sternal bands of screw tail and normal mice are similar although the diffuse mesenchymatous condition of the structures does not readily lend itself to a precise determination of size. Screw tail animals cannot therefore be recognized by the sternum, but must be identified by other phenotypic manifestations of the gene that go further back into the embryological history. Mutant mice can best be separated from their normal litter mates by the length of the tail, which at 13 days reaches well beyond the tip of the maxilla in normal, but not in screw tail animals. By the fourteenth day no difficulty is encountered in distinguishing the sternum of the screw tail embryo, either in sectioned material or in cleared dissections from which the pectoral musculature has been removed (compare figs. 5 a and b). The sternal bands of mutant embryos are wider than normal, particularly at the anterior ends where union is to begin. Laterally the bands appear drawn out at the sternocostal junctions as though under tension and again the effect is most marked anteriorly, with the second and more rarely the third rib occasionally torn away as previously described in adults by MacDowell et al. ('42).

Omitting momentarily a consideration of the sternum proper, it is an unmistakable fact that in the embryo and adult screw tail mouse the ends of the costal cartilages at their junction with the sternum do not come as close to the median sagittal plane as in normal animals. For example, the intervening transverse distance between the tips of the third costal cartilages is relatively great in a screw tail animal. It is recalled that the presternal elements and sternal bands are at first widely separated laterally but grow continuously closer together in the

ventral midline in synchrony with the growth of the ribs and clavicles. Growth of the ribs appears to be retarded in screw tail mice, whereas clavicular and omosternal growth is relatively normal (fig. 5).

The dissections shown in figure 5 were made by removing the anterior portion of the thorax of $14\frac{1}{2}$ -day Zenker fixed embryos, staining in Toluidin blue, dehydrating, and clearing in methyl salicylate. All musculature was removed down to the level of the intercostales externi. In both specimens the two omosternal cartilages were firmly affixed to the sternal bands through contact with the presternum and joined

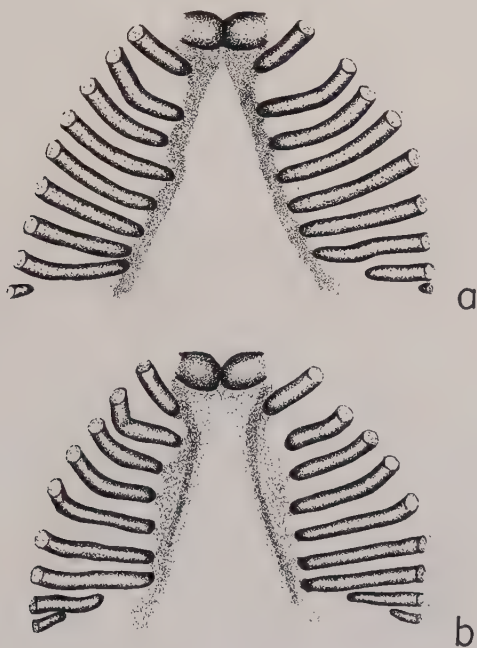


Fig. 5 Inside view of dissections of the anterior chest wall of $14\frac{1}{2}$ day $\pm \frac{1}{2}$ hr. sibling embryos; (a) normal, and (b) screw tail. Camera lucida. 35 $\times$.

medially. Either through a difference in degree of curvature or in growth, the third and fourth costal cartilages on the left side of normal animal (a) afford an interesting comparison. Tension has been placed on the lateral margin of the sternal band by relative retardation of the third rib. In contrast the fourth rib is well advanced and has pushed its way into the cartilage of the sternum, resulting in a pronounced inward curve in the disposition of the sternal band. There is a difference in the relative growth of the eighth ribs, but altogether the sternal bands present a compact appearance.

When attention is turned to the screw tail sibling, a modification of the normal pattern is obvious (fig. 5 b). Although the mutant animal is only 0.8 mg. heavier than its litter mate and therefore serves as a valid standard of comparison, the ends of the ribs are further apart. Furthermore, the lateral margins of the sternum show distinct evidence of rupture at the sternocostal junction of the second rib on the right side. Failure of rib ends to approach the midline may be regarded as contributing to the lateral drawing out of sternocostal junctions in screw tail embryos as seen in figure 5. The effect is described as one of tension. It should be emphasized that the sternal bands of screw tail and normal mice appear identical, at least until the period when rib differences of the type observed in figure 5 must be initiated at the end of the thirteenth day. Broken sternocostal junctions of second and third ribs are never seen until the fourteenth day and hence must be secondary, probably originating through tension produced by relative growth disharmony between the two fundamental anchorages of the sternal bands, i.e. the abnormal ribs and the relatively normal pectoral girdle. Failure of the sternum to tear away from the first pair of ribs depends on the greater width of the manubrial primordia; an accurate reconstruction to scale (123X) of ribs, sternal bands and clavicles, showed the manubrial precartilages held against the first ribs by extension of the lateral manubrial margin along the omosternal elements, both in screw tail and in normal mice. The same contiguity of presternum with the first ribs is revealed by dissections in figures 8 and 9. Among screw tail embryos it would be expected that the opposing stress of ribs and clavicles would become progressively less evident at the more posterior sternocostal junctions. This is clearly suggested by comparing figures 13 and 15. Apparently the major role in moving the sternal bands together in screw tail animal devolves upon the clavicles, whose growth and development is comparatively normal.

In addition to the appearance presented by dissected specimens, other evidence points to both tensile and compressive effects of rib ends on the lateral margins of the sternum: (1) histologically the cartilage cells are more compressed at the sternocostal junction of normal as compared with screw tail mice; and, (2) at the level of the second rib close conformity exists between the normal sternum and the rounded head of an advancing rib (figs. 10 and 12). In screw tail animals sternal configurations at the same thoracic level suggest that the sternum is being subjected to lateral tension (figs. 11 and 13), or that a rib has been broken away.

ANALYSIS OF RIB GROWTH

One result of the screw tail mutation is a decrease in length of individual vertebrae, with a consequent shortening of the tail first seen in 13-day embryos. Among adult screw tail mice the two or three caudal vertebrae missing from the tail tip of a typical animal are insufficient to account for the marked relative foreshortening of the axial skeleton, secondarily obscured by coiling of the tail. Vertebrae are sometimes wide, particularly where ventral ossification is defective, but it is certain that many are growth deficient. Since in contrast to the clavicles, the ribs are derivatives of the axial skeleton and grow out from the vertebrae, it is suggested that they also are growth deficient. This essential point can be tested in two ways.

In order to compare rib growth in screw tail and normal animals, dissections of the type shown in figure 5 were made of the embryos of fifteen litters from heterozygous parents. Mothers were sacrificed at $14\frac{1}{2}$ days $\pm \frac{1}{2}$ hour from the time of mating and the young removed from the uterine horns and fixed in Zenker. After staining in 0.5% Toluidin blue, or in Delafield's haematoxylin for smaller specimens, the dissections were dehydrated in alcohol and cleared in benzene and winter-green oil. Of 139 embryos, 23 were resorbed, 5 were small and could not be identified, and 4 normals were torn in dissection and discarded. The remaining 107 embryos comprised a total of 78 normal to 29 screw tail animals. Including the 4 normal embryos injured in dissection, the ratio of normal to screw tail in these segregating litters obtained from heterozygous Balb screw parents was 2.8 to 1, an insignificant departure from a 3:1 ratio. Litters from heterozygous parents but containing no screw tail embryos were included in the total. After fixation in Zenker and washing, all embryos were weighed to within $\frac{2}{10}$ mg. The cube root of embryo weight in milligrams can be correlated directly with growth in linear dimension of the rib.

In figure 6 curves are given representing the transverse distance between the ends of two pairs of ribs, the second and seventh, for 107 embryos taken $14\frac{1}{2}$ days $\pm \frac{1}{2}$ hour from the time the mother was mated. The mean weight of seventy-eight Zenker fixed normal embryos was 142.9 ± 2.6 mg. and for twenty-nine screw tail sibs was 140.0 ± 5.0 mg. The difference is insignificant ($P > .5$), but may not be taken as evidence in comparing the skeletal weight of normal and screw tail mice; in new born rats the skeleton comprises but 10% of the total body weight (Donaldson, '19). Therefore all embryos were placed in five separate weight categories on the assumption that individuals of approximately the same weight were most nearly alike in physiological

age and degree of development, regardless of genotype. In this manner a direct comparison of rib growth in normal and screw tail embryos was made.

The ends of the ribs grow toward the midline and come closer together as the embryos become larger. It will be observed that in any given weight category the second rib ends are closer together than the seventh, indicating that the sternal bands are moved together as a V, with the apex directed anteriorly and the apical angle constantly being reduced. A significant difference exists between screw tail and normal animals in the distance intervening between the approaching ends of the second ribs in every weight group except the smallest, and the same

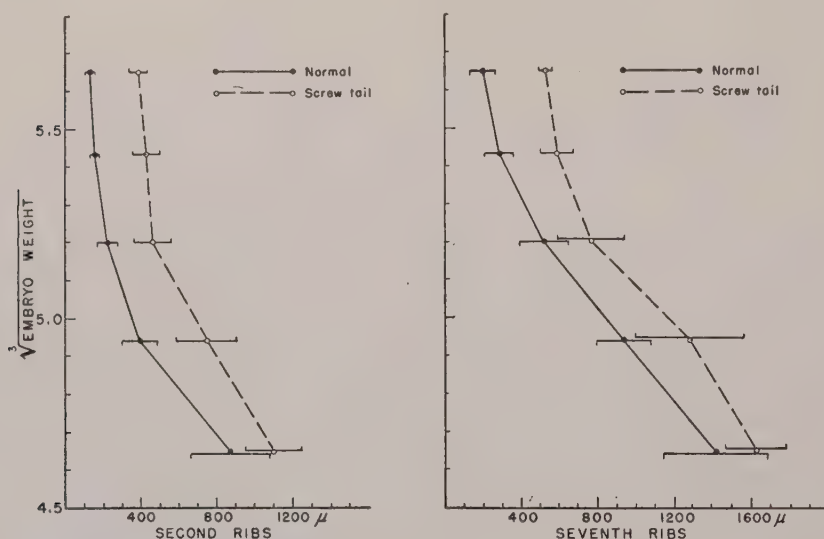


Fig. 6 Transverse distance between the tips of the second ribs, and also between the seventh ribs of normal embryos (solid line), and of screw tail embryos (dash line), aged $14\frac{1}{2}$ days $\pm \frac{1}{2}$ hr.

fact is apparent among larger animals when the seventh ribs are compared. Standard errors are represented in figures 6 and 7 by horizontal bars, the total length of each bar being twice the standard error of the mean. Among smaller embryos the lack of concise phenotypic distinction between the ribs of mutant and normal animals is doubtless due to the effects of individual variability which tends to swamp phenotypic difference until the limits of growth imposed by the genotype become evident. Presumably the effect of the mutation is upon growth rate, although the curves do not diverge significantly and a difference in the time of onset of growth can not be eliminated.

A demonstration that the ribs of screw tail animals are further from the median line at specified stages of development is suggested to bear a causal relationship to the determination of the mutant sternal pattern. Additional evidence exists that the ribs of screw tail embryos are really smaller than normal and that the greater distance separating the rib ends of mutant animals is not due merely to alterations in the angle of curvature or general shape of the thorax. A quantitative difference between mutant and normal ribs in animals of the same stage of development is shown by determining rib volume directly. Volumes

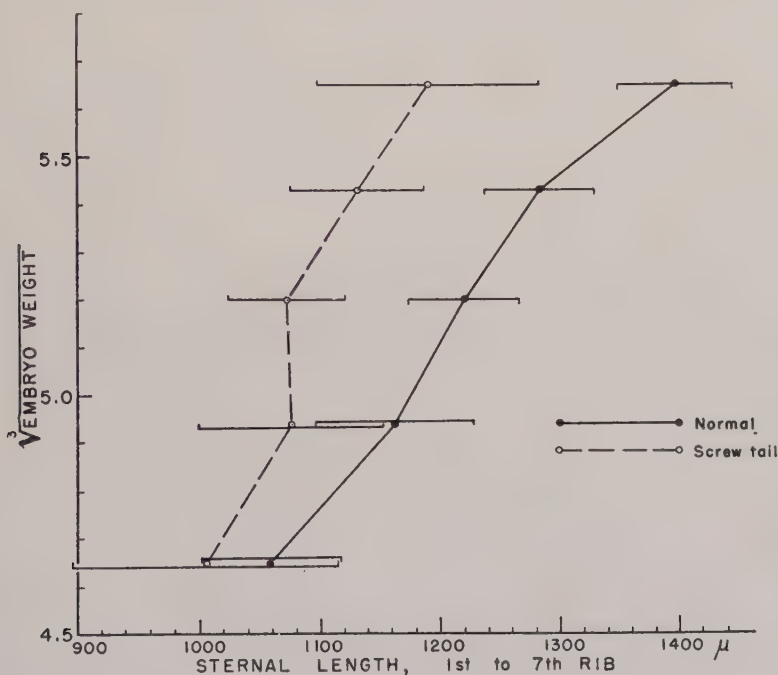


Fig. 7 Longitudinal distance between the sternocostal junctions of the second and seventh ribs of normal embryos (solid line), and of screw tail embryos (dash line), aged $14\frac{1}{2}$ days $\pm \frac{1}{2}$ hr.

of the first six pairs of ribs were calculated from the weight of cut out camera lucida drawings made from serial sections of embryo at a magnification of 126 diameters. Two siblings of $14\frac{1}{2}$ days were compared, a normal weighing 145 mg. and a screw tail weighing 147 mg. The smallest, or first rib pair, had a combined volume of .025 cu. mm. in the screw tail and .032 cu. mm. in the normal sibling. Each pair of ribs was larger in the normal animal, ranging up to .075 cu. mm. with a value of .056 cu. mm. for the same (sixth) pair in the mutant. It is pos-

sible, though not demonstrated, that the marked reduction in volume of the mutant ribs is dependent on decreased diameter as well as length. A volumetric analysis can only supplement the data presented graphically in figure 6, upon which the conclusion is based that the great width of the sternum in screw tail mice and the failure of some of the ribs to maintain contact with the sternum is not a primary effect of the screw tail mutation, but is a secondary consequence of growth retardation in the ribs of screw tail animals.

LENGTH OF THE MUTANT STERNUM

Initial morphological modification

Increased width of the mutant sternum is accompanied by a decrease in length. At 14½ days the sternal bands are undifferentiated bars of cartilage with no trace of the future centers of ossification. It is difficult to measure the length of the entire sternum exactly because the posterior margin of the prospective xipoid process becomes gradually more diffuse, having no well differentiated margin; and the anterior margin of the manubrium is intimately fused to the omosternal cartilages. One may observe that the mutant sternum is about the same length as normal anterior to the first pair of ribs and slightly shorter posterior to the seventh in the region of the future xipoid process. Two well defined anatomical landmarks serve for more exact measurements: the union of first and seventh pairs of ribs with the sternum. As this distance is shorter in screw tail embryos (fig. 7), the sternum must be shorter in its entirety.

Lack of segmentation

Since the sternum of the screw tail mouse never develops epiphyseal cartilage zones that normally provide for longitudinal growth, it becomes a single large bone rather than a series of six individual small bones. Failure of the mutant sternum to grow to normal length is therefore related, at least in part, to lack of segmentation; a later problem ontogenetically and one with a cause yet to be ascertained. In the adult screw tail animal the highly shortened sternum is attributable to failure in developing separate centers of ossification, with the result that bone growth is predominately appositional and lacks the longitudinal growth normally afforded by eight sternal epiphyses.

Reference to figures 16-21 shows that the influence of costal cartilages upon the sternum is to delay ossification at the region of contact both in the mutant and normal structure. In normal animals (figs. 16 and 17)

the onset and spread of ossification in the sternum is limited by the opposing zones of inhibition which, through normal growth of the ribs, have come in contact in the midline establishing a barrier that will become a joint if there is an ossification center on either side of it. In screw tail animals (figs. 18 and 19) the paired zones of inhibition are so widely separated through deficient rib growth and subsequent great width of the sternum, that the paired areas of immature cartilage do not meet in the midline except in the region of the xiphoid process. Consequently ossification proceeds uninterruptedly throughout the length of the sternum, resulting in the formation of a single bone instead of the six separate bones of the normal mouse.

The ossifiable sternal cartilage and the non-ossifiable costal cartilages are directly connected by a continuous matrix through which at least some substances involved in the initiation and maintenance of ossification may be assumed to be diffusible. Now there is known to be a biochemical difference between ossifying and non-ossifying cartilage. Fell and Robison ('30) examined endochondral ossification in the chick, finding that the chondroblast hypertrophy normally preceding ossification is associated with a sharp rise in phosphatase, as determined by the hydrolysis of glycerophosphoric ester. In the unossified costal cartilage of the 27-day-old rat, Robison ('32) found almost no evidence of phosphatase activity.

An analysis similar to that of Robison was made on screw tail and normal embryos aged 15 to 18 days, utilizing the technique devised by Takamatsu ('39) and Gomori ('39). Sections were incubated with calcium ions in the presence of buffered sodium glycerophosphate at 37°C. Later the transfer to 2% cobalt nitrate, followed after washing by dilute iron sulphide, resulted in the deposition of cobalt sulphide as an indicator of phosphatase activity. Controls were run concurrently.

Only in prospective or actual ossification centers of the sternum could phosphatase be found to any degree (fig. 2). The concentration of phosphatase was invariably reduced in the costal cartilages and, probably as a result, in the contiguous cartilagenous areas of the sternum. Since calcium salts and perhaps other substances directly concerned with the metabolism of bone may exhibit a similar gradient of concentration, it is not proven that phosphatase is the only factor or even the main factor involved in the establishment of sternal pattern. But by modern conceptions of the biochemistry of bone formation, the role of phosphatase is important, and its reduced concentration at the ends of the costal cartilages is possibly related to the inhibition of ossification at the sternocostal junctions of both screw tail and normal mice.

OUTCROSSING OF THE BAGG ALBINO SCREW TAIL STRAIN

If the failure of joints to form in the sternum of the screw tail mouse is the direct result of reduced rib growth, it should occasion no surprise when the same type of pattern occurs in mice of non-screw genotype as a developmental accident. Union of two sternebrae into one wide bone without any vestige of a connecting articulation is sometimes seen in normal mice correlated with local reduction in the length of the ribs (MacDowell, unpublished). Conversely, a modification of the effects of the gene toward wild type, possibly attainable by outcrossing, might allow articulations to form in the sternum of the screw tail mouse. This was in fact realized in the F_2 generation of matings of heterozygous CSH Bagg albino screw tail mice by (1) Storrs Little, and (2) short ear. The suture observed between the third costal cartilages of an out-cross animal (fig. 3) represents a phenotypic shift toward wild type, resulting from a change in the residual heredity. In general an articulation forms only when the costal cartilages end close to the medial line of the body. In F_2 animals homozygous for both screw tail and short ear factors, the independent effect of short ear in reducing the length of the xiphoid process (Strong, '34) was not obscured.

DISCUSSION

Variations in the form of the sternum are encountered frequently among animals, both as developmental abnormalities and as interspecific differences (Hanson, '19). Deviations from normal development offer abundant material for studies of the relationship of ribs and sternum (Shaw, '29; Green, '39). In the mouse ultimate union of the paired primordia of both sternum and pectoral muscles would seem to depend on the normal growth of both ribs and clavicles, although in some mammals (pig, whale) the growth of one of the two agents is alone effective in bringing the sternal anlagen into their definitive position. A dependence of sternal union at the midline upon rib growth is apparent in cleft sternum, first described in the pigeon (Chevalleraie, 1740, cf. Greig, '26) and seen among humans in frequent association with ectopia cordis. A less extreme modification of rib growth results in the persistence of a small perforation in the human gladiolus, representing the original interband space (Stieve and Hintzsche, '25).

Equally important is the effect of the ribs in determining a pattern of sternal segmentation. In all mammals including man, ossification centers of the sternum bear a constant relation to the position of the ribs. Even if the mesosternum is to be a single bone (i.e. the gladiolus),

separate centers may be present originally which never arise except in the regions of the sternum that lie intercostally. The elements of the sternum may remain separate after birth as in the mouse or may fuse at different periods of life as in the human. But in all mammals the invariable rule may be stated that sutures or articulations will be found only where sternum and ribs come in contact.

Hanson ('19) has observed that the points of junction of ribs and sternum are usually narrow and give the appearance of structural weakness. Strains are assumed to exist in the embryo, and "sutures arising in this manner as a result of strain will naturally appear at the weakest parts along the sternum". This point of view is questionable for several reasons: (1) The wax model used by Hanson to test the theory could not be assumed to have the same physical properties as the embryonic sternum, and was in all probability more rigid as indicated by its fracture upon bending; (2) no stresses are known which would bend the embryonic sternum to any degree; and (3) at least in the mouse the appearance of sutures or articulations is a much later event developmentally than the onset of intercostal ossification and the determination of sternal pattern.

However this may be, the location of articulations and epiphyses in the normal mouse sternum is always directly between the costal cartilages of two bilaterally opposite ribs, usually members of a pair. Normally the onset of ossification within the sternum is midway between the sternocostal junction of one pair of ribs and an anterior or posterior pair (fig. 4 d). This is generally true for all animals that have been examined (Hanson, '19).

What is it that determines where the ossification centers will be found, and where the persistent intervening barriers of cartilage (which in the mouse develop into articulations) will be located? Location of the ribs seems of primary importance, yet the position of future joints might be determined embryonically in the sternal band even before ribs and sternum come in contact. Experiments of Fell and Canti ('34) on development of chick long bones *in vitro* indicate that indifferent cartilage will form a joint if it is placed between two centers of ossification, but the original joint will not develop if excised. Hence self differentiation can be ruled out in the formation of an articulation. Whether this view can be applied to the mouse is problematical. It would appear from the researches of Carey ('21), as well as Fell and Canti ('34) that the essential embryonic prerequisite for the formation of a joint may often be the existence of a neutral layer of cartilage which must become impinged between the expanding concavities of two opposed and growing

diaphyseal bone centers. No definite rule can be made, as is shown by the formation of sternochondral joints in the 3½-month human fetus directly in cartilage (Gray and Gardiner, '43).

In the mouse, location of ossification centers is of primary importance, and it may be shown that this is not predetermined in the sternal bands but depends upon contact with the ribs. Immature cells are grouped at the sternocostal junctions and the hypertrophy of chondroblasts initiating ossification begins in the sternum half way between one pair of costal cartilages and another. The effect of costal cartilages in determining where ossification will be retarded is observed even when the union of ribs and sternum is modified appositionally (MacDowell et al., '41-'42) and is shown for different types of mice in figures 16-21. Since the sternal bands are evidently of equal length in individuals showing appositional disharmony (figs. 20 and 21), it may be concluded that the determination of ossification pattern occurs after the union of ribs and sternum and is due directly to an inductive effect. Regions of the sternum furthest from the ends of the ribs are those in which the chondroblasts first begin to hypertrophy, marking the future centers of the sternebral diaphyses and determining by their growth where the future articulation will be.

When considered in conjunction with the sternal pattern of outcross screw tail mice, particular significance is attached to a condition found normally in the gibbon and as a rare anomaly in man; described as extension of the presternum to the third costal cartilages (Dwight, 1890). The human condition is invariably marked by a failure of the second costal cartilages to come within normal proximity with attendant failure of the normal suture to form. In contrast, the third costal cartilages, marking the displaced suture, extend abnormally close to the sagittal plane. Also in man the original sutures in the gladiolus (mesosternum) present at birth become obliterated during growth in direct proportion to the transverse distance between the ends of the ribs. This would be expected if determination of pattern is causally related to the transverse proximity and position of the costal cartilages.

Some latitude is evidently possible in the dependent relationship of sternal segmentation pattern to the ribs. Green has examined races of rabbits possessing an extra pair of ribs and found that only 31% of the 107 animals with 13 ribs also possessed an extra sternebra. Failure of an additional sternebra to form invariably is probably related to variations in the degree of crowding of costal cartilages at the posterior (xiphoid) end of the sternum. The inhibiting effect that crowding produces upon ossification is seen in figures 16 and 18. Anteriorly, as the

ribs become more widely spaced, ossification is progressively more extensive. In brief, the same principle of delayed or completely inhibited ossification in regions adjacent to costal cartilages pertains when considering the antero-posterior axis that has been considered more fully with reference to the transverse axis.

Considered phylogenetically, the same dependence of sternal ossification upon the ribs is noted. If costal cartilages fail to reach the sternum, the mesosternum is unsegmented, even if the sternum itself is narrow as in the reptile *Chirotos*. More commonly when the ends of the ribs do not come close to the sagittal plane, the sternum is broad. It may then be unsegmented (as in the manatee and Bagg albino screw tail mice) or with closer proximity of the costal cartilages segmentation is poorly developed (as in man and outcross screw tail mice). When the costal cartilages extend almost to the midline, segmentation is well developed unless the sternum lacks the capacity for ossification. Some species variability is to be expected that is not entirely dependent on the inhibitory effect of costal cartilages upon ossification.

We have seen that in mice the ribs begin growing out from the thoracic vertebrae during the twelfth day, at the same time that a difference in tail length between mutant and normal animals is becoming established. Embryologically the approximation of the first and seventh pairs of ribs in screw tail animals must originate from a decreased distance between myosepta in which the ribs arise before their union with the sternal bands. Where somite number is not greatly diminished, reduced tail length must also be a function of decreased distance between myosepta. Both rib and tail abnormalities; reduction in size of certain head bones; shift in the relative position of the pelvic girdle, as well as numerous other characteristics of the screw tail mouse noted by MacDowell et al. ('42) appear to originate through a general mesodermal growth deficiency of the axial skeleton beginning at the twelfth day, and producing indirectly a modification of sternal pattern by way of the ribs. When considered with reference to a selective system of skeletal growth retardation, such seemingly unrelated effects as the short tail, the abnormal position of the pelvis, and lack of segmentation of the sternum are fitted together developmentally. Their further study should lead to added information concerning the substances and conditions necessary for normal growth of cartilage and bone.

SUMMARY

An embryological analysis is made of sternal development in normal mice, and in others homozygous for the screw tail gene.

The sternum originates on the twelfth day as paired bands of pre-cartilage which grow caudally from the shoulder girdle and later join secondarily to the ribs. Movement of the sternal bands to the median plane, effected by growth of the clavicles and ribs, is terminated during the fourteenth day.

In animals otherwise homozygous for the CSH Bagg albino genotype differences between the normal and mutant sternum involve (1) greater width of the mutant structure, and (2) absence of segmentation correlated with reduced growth in length.

Greater width of the sternal bands in screw tail mice can be seen at the onset of the fourteenth day, before the bands have united medially. The increased width is due to relatively normal growth of the clavicles accompanied by growth retardation of the ribs. The resultant lateral tension where ribs and sternum join produced a mechanical strain with frequent rupture of union in the region of the second and third costal cartilages.

Increased width of the sternum is not, therefore, a primary effect of the gene, but is secondarily the result of growth retardation of the ribs. The latter is one manifestation of gene action on the axial skeleton in general, first noted at the thirteenth day by a shortening of the tail dependent upon a reduction in the size of the vertebrae, possibly including those from which the growth deficient ribs are derived.

Lack of segmentation of the sternum in Bagg albino screw tail mice is a direct consequence of retarded rib growth with increased sternal width. Regions of the sternum in contact with the ribs exhibit delayed ossification and the maintenance of a region of immature cartilage within the sternum proper, near the ends of the costal cartilages.

In normal animals these areas of delayed ossification meet in the sagittal plane, determining the location of joints and dividing the sternum into a series of separate bones that develop epiphyses and grow longitudinally.

Because of reduced rib size, areas of delayed ossification in the sternum at the ends of the costal cartilages fail to meet medially in Bagg albino screw tail animals. As a result bone develops continuously through the entire length of the sternum, precluding the formation of articulations, and limiting future growth to the appositional deposit of periosteal bone with relative reduction of sternal length.

Some evidence is presented to indicate that the regional determination of ossification centers in the sternum may be due to a diffusion of phosphatase out of the sternum by way of its matrical continuity with the non-ossifying costal cartilages.

F₂ mutant animals from outcrosses of CSH Bagg albino screw tail mice of two unrelated lines show that the screw tail mesosternum may become segmented, representing a modification toward wild type. Articulations appear to form because of reduced distance between the right and left members of a pair of costal cartilages.

Significance of the findings is discussed as applied to interspecific and phylogenetic variability of sternal pattern.

It is a pleasure to acknowledge the continued interest and advice of Dr. E. C. MacDowell, at whose invitation this work was undertaken and by whom many of the basic observations were first made. The technical assistance of Miss E. N. Ward is also gratefully appreciated.

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PLATE 1

EXPLANATION OF FIGURES

- 8 Normal embryo. Age 15 days. Dissection of alcohol fixed specimen stained with Toluidin blue. 24 X.
- 9 Screw tail embryo. Age 15 days. Note sternum torn away from second and third costal cartilages. 24 X.
- 10 Normal embryo. Age 14½ days. Frontal section. Second ribs closely opposed to sternal bands. ST.B., sternal band. R.2, end of second rib. 34 X.
- 11 Screw tail embryo. Age 14½ days. Frontal section. Ends of second ribs fail to reach sternal bands. 34 X.
- 12 Normal embryo. Age 15½ days. Frontal section. Sternum compressed inward by second rib because opposing stress is not offered by slightly misplaced partner on opposite side. 34 X.
- 13 Screw tail embryo. Age 15½ days. Frontal section. Sternum under tension laterally by both second ribs. Observe sternal hyperplasia which is not yet evident in figure 6 d. 34 X.
- 14 Normal embryo. Age 16 days. Frontal section. Onset of cartilage hypertrophy is located intercostally. 117 X.
- 15 Screw tail embryo. Age 15½ days. Frontal section. Same individual as figure 13 but with section through posterior end of mesosternum. Medial compressive influence of the ribs is seen, even in a screw tail animal, as distance from the clavicles is increased. 34 X.

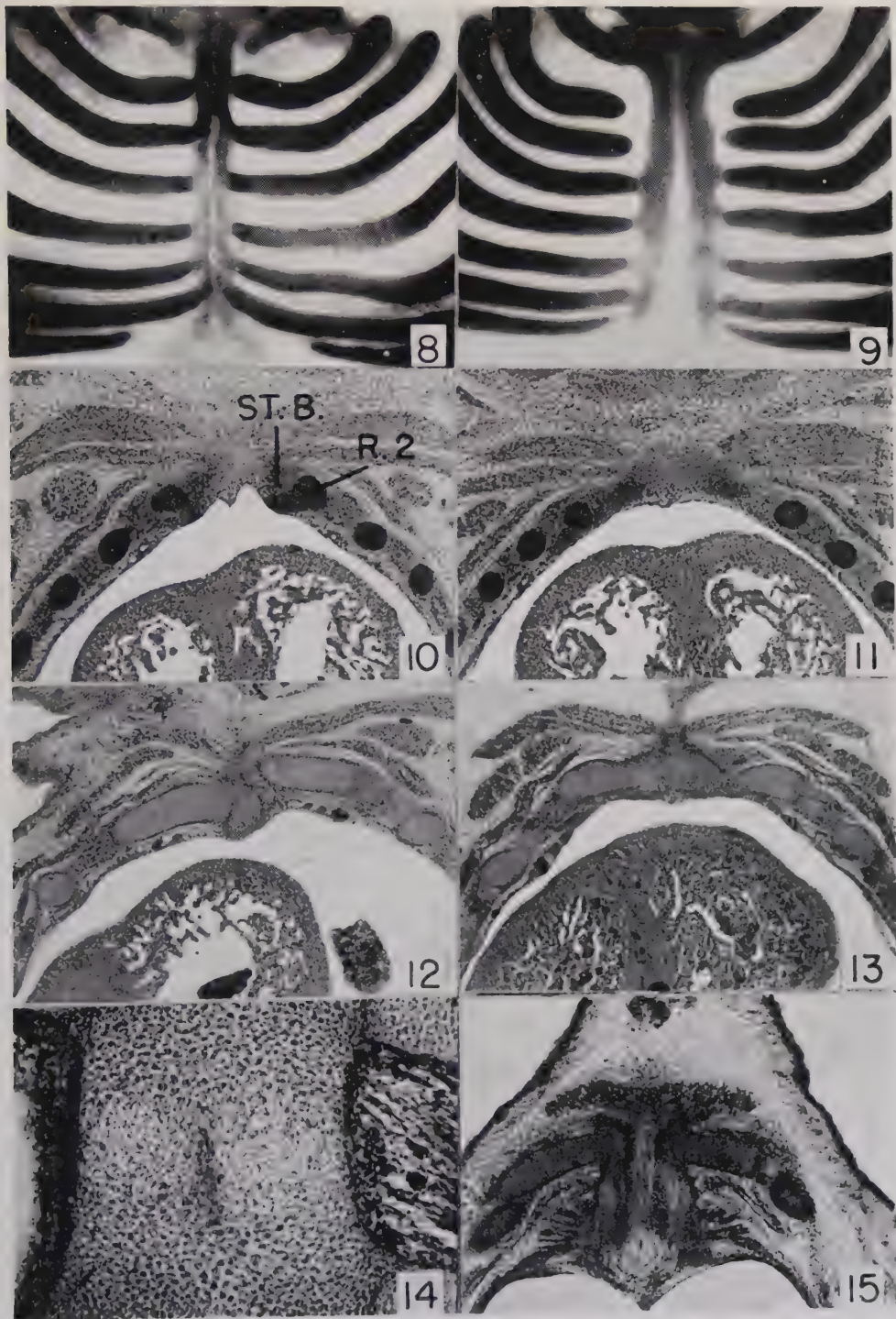


PLATE 2

EXPLANATION OF FIGURES

16 Dissection of anterior chest wall of a new born normal animal. Ossification is inhibited at the regions where sternum and costal cartilage meet; resulting in transverse bands of cartilage across the sternum and delimiting the site of future articulations. 8 X.

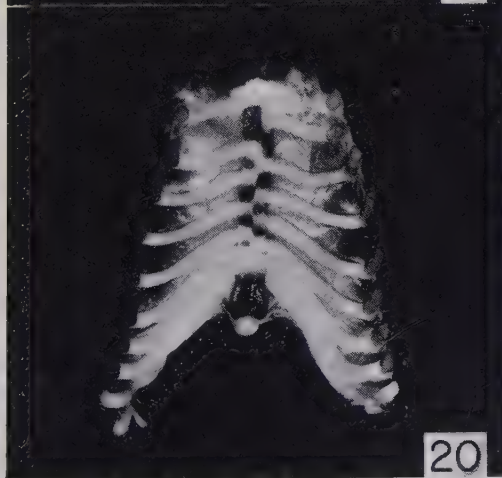
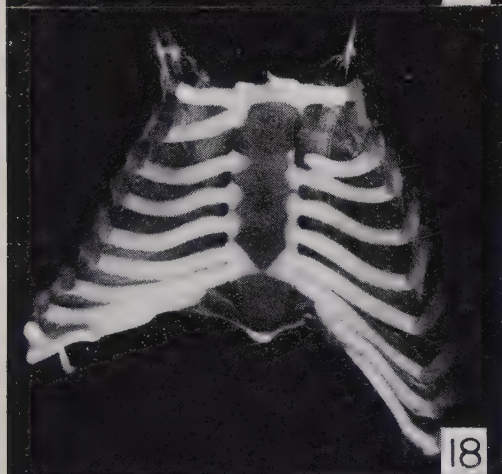
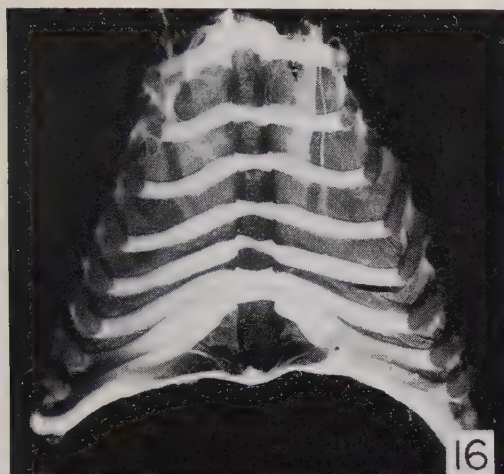
17 Sectioned sternum. New born normal animal. Immature areas of sternal cartilage extend between the costal cartilages of each pair of ribs. 14 X.

18 Dissection of a new born screw tail animal. Due to great width of the sternum, areas of immature cartilage fail to meet medially. Complete ossification of the sternum results. Observe inhibition even where second rib has torn away. 8 X.

19 Sectioned sternum. New born screw tail animal. Histological evidence for regional inhibition of sternal ossification at the sternocostal junctions is clearly seen. 14 X.

20 Dissection of a new born abnormal animal of presumably normal genotype. Right costal cartilages are shifted forward. Inhibited areas are distributed in secondary conformity to the original developmental accident. 8 X.

21 Sectioned sternum of a new born animal exhibiting the same abnormality shown in figure. Checkerboard pattern results from the embryonic determination of ossification centers in regions not adjacent to costal cartilages. 14 X.



NEW DATA ON THE ORIGIN OF DOUBLE AVIAN EGGS

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THREE FIGURES

A number of double eggs of the general class, ovum in ovo, have been recorded. Most of these have been obtained from the domestic fowl (see reviews by Davaine, 1861; Parker, '06; Curtis, '16; and Asmundson, '33), but they have also been produced by the turkey (Panum, 1860), the duck (v. Frankenberg, '28), and the goose (Hahn, '30). There are numerous variations in the structure of these double eggs. Curtis ('16) classified them in two main groups as follows: (I) double eggs in which the enclosing egg is complete with yolk; and (II) those in which the enclosing egg lacks a yolk, but is otherwise complete. Each of these classes she again divided into two sub-divisions according to whether the enclosed egg is (a) complete with shell and yolk, or (b) a dwarf egg.

Perfect double eggs of the type Ia in the classification of Curtis, are apparently comparatively rare. She herself described two such specimens as did Roberts and Card ('29). Others have been reported by Henneguy ('11), Patterson ('11), and Asmundson ('33), and there are other scattered references to the same type of doubling in the voluminous literature on abnormal eggs. Davaine (1861) cited thirty-eight reports of double eggs but knew of only four cases in which the enclosed egg was known to contain a yolk. It seems desirable, therefore, to report a case in which one hen laid no fewer than ten, and possibly more, complete double eggs in which both the large enclosing egg and the one included had all component parts present. Moreover, the fact that this bird was one of a flock at Cornell University from which trap-nest records of egg production were being obtained resulted in somewhat more data being available than for the sporadic cases previously reported.

OBSERVATIONS

The record

The ten double eggs were laid by K 304, a 1-year-old Single Comb White Leghorn hen, during May, June and July of 1943. Their distribu-

tion is shown in figure 1. An egg broken in the nest on May 9th was probably of the same type, since a normal egg was surrounded by albumen and the remnants of a thin outer shell. It will be noted in figure 1 that of these eleven double eggs not one was preceded by an egg on the previous day, although two were followed by an egg on the next day. The modal interval both before and after a double egg was 2 days.

Although K 304 was apparently normal in most respects till shortly before her death, her egg-record showed that she was not only sub-normal in egg production, but also given to laying soft-shelled eggs. She began laying at 185 days of age, but after laying sixteen eggs in

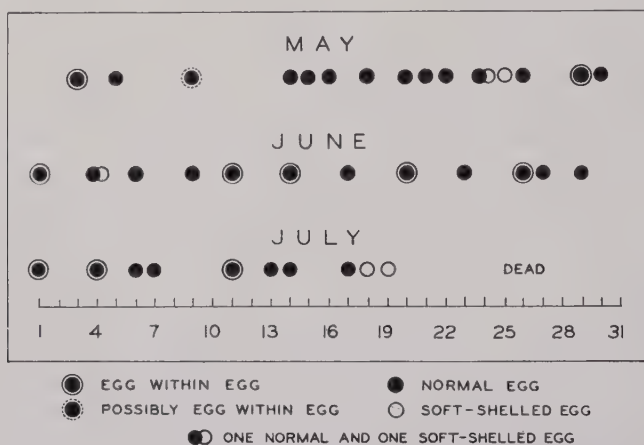


Fig. 1 Distribution of eggs laid by K 304 during May, June, and July, 1943, showing the spacing of single and double eggs. Single eggs were laid on the days following the double eggs of May 29th and of June 26th, but no eggs were laid on the days preceding the ten double eggs, the probable double egg of May 9th, or the two eggs laid on May 24th and on June 4th.

October, '42, ceased laying until January 29, '43. During early February, three broken eggs (indicating thin shells) were recorded and one soft-shelled egg. Two more broken eggs were charged to her in April. From January 29th to April 30th (when the record of fig. 1 begins) she laid only thirty-one eggs, somewhat less than half of a normal production for that period. More soft-shelled eggs were laid in May, and again on July 18th and 19th. It is quite probable that other soft-shelled eggs were laid outside of the trapnests (as frequently happens with such eggs) and hence are not credited to K 304's record. Death, on July 26th, was attributed to peritonitis and no gross abnormalities of the reproductive tract could be detected.

Orientation of the eggs

Through the window made in the large egg (fig. 2) one can see that the enclosing egg was complete with shell, membranes, albumen and yolk. The yolk appeared to be distorted in shape because of the pressure exerted upon it by the hard shell of the enclosed egg. This, the inner egg, was of normal shape and very large. In the egg shown in figure 3, and in those of the others in which blunt and sharp ends could be distinguished, the contained egg lay in the blunt (larger) end and the yolk in the smaller end.

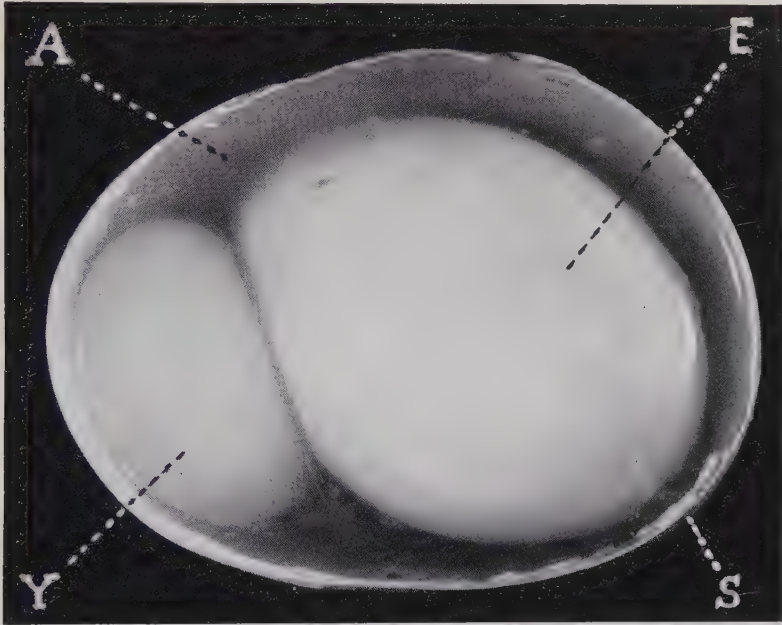


Fig. 2 Appearance of the opened double egg. A — albumen; E — enclosed egg; S — shell with membranes; Y — yolk.

In every case both the contained egg and the yolk were rather firmly embedded in a single mass of albumen which surrounded the two as if they were one object. This fact, which is important in determining how double eggs are formed, was more evident in the ones under discussion than in most of the other cases reported in the literature, possibly because those of the present series were all examined within a few days of their being laid. In many of the double eggs previously described, some or all of the albumen had been lost before the egg came to the investigator who described it, while others had been held long

enough to cause some liquefaction of the firm albumen which normally comprises the inner layer surrounding the yolk, the contained egg, or both.

In the present cases, so closely were the contained egg and the yolk held together by the firm albumen that it was difficult to change the position of some of the contained eggs which lay, like that shown in figure 2, with the long axis at an oblique angle with the long axis of the big enclosing shell. This means that both enclosures were enveloped at the same time, and hence, since the dense albumen is secreted only in the albumen tube, that the contained egg must have gone back when fully formed to the albumen-secreting region of the oviduct where it met the new yolk.

In most cases, the long axis of the contained egg coincided with that of the big outer shell, but in two of the ten eggs, one of which is shown in figure 2, the long axis of the contained egg lay at an angle. Unfortunately, it was impossible to distinguish with certainty a large and a small end of the enclosing egg, except in four cases. The air cell, which is usually found at the blunt end, was on the side in all double eggs. These four, however, did yield considerable information about a problem that has bothered previous investigators, namely, the orientation of the contained and the enclosing eggs. In two of them the small end of the enclosed egg pointed in the same direction as the small end of the outer shell, as Parker ('06) found in all double eggs known to him. However, in two others this situation was reversed and the sharper end of the enclosed egg was directed toward the blunt, larger end of the outer shell. These relationships are shown diagrammatically in figure 3. It should be noted that in all four cases the yolk was in the smaller end of the big egg. The significance of these facts will be discussed later.

Structural characteristics

The double eggs ranged in weight from 170.1 to 192.9 gm. While those weights are from 3 to 3.5 times the weight of a normal hen's egg of 57 gm., they are only 2.4 to 2.8 times that of the 70-gm. eggs which K 304 laid singly in between the double eggs. Details of the component parts are given in table 1, which shows the averages for a number of weights and measurements of the enclosing egg, the enclosed egg, and single eggs laid by the same hen.

While the abnormalities of the big outer eggs are striking, it must be remembered that they are merely the inevitable result of the effort on the part of the oviduct to secrete albumen, membranes and a shell

over any object, large or small, that passes through. Thus, while the excessive amount of albumen (78.66 gm.) was about four times the weight of a single yolk, whereas in single eggs the ratio of albumen to yolk was only 2.6 to 1, this resulted merely from the fact that the stimulus to secretion of albumen was provided in the double eggs, not by a yolk alone, but by a yolk plus a complete egg. The extremely weak shells of double eggs have been noted in previous reports. In this case, they were even weaker than is indicated by the shell thickness in the three classes of eggs, and, as a result, it was impracticable to determine their breaking strength by the same technique as was used for the others.

TABLE 1

Average characteristics of double eggs and of those laid singly by the same hen.

ITEM MEASURED	DOUBLE EGGS		SINGLE EGG			
	Enclosing egg	Enclosed egg				
Number of observations	5-7	4-10	4-6			
Weight (gm.)	106.75	75.00	70.01			
Total weight (gm.)	181.75					
Circumferences (mm.)						
Long axis	224	165	163			
Short axis	195	148	146			
Length (mm.)	80.8	58.1	57.4			
Breadth (mm.)	62.0	46.8	46.6			
Ratio: Breadth/Length $\times$ 100	70.45	80.55	81.27			
Thickness of shell (mm.)						
Pointed end	0.19	0.27	0.225			
Blunt end	0.22	0.22	0.21			
Breaking strength of shell (kg.)	very weak	2.12	1.50			
	gm.	%	gm.	%		
Albumen	78.66	73.7	50.67	67.6	46.25	66.1
Yolk	19.82	18.6	19.20	25.6	19.42	27.7
Dry shell, with membranes	8.27	7.7	5.13	6.8	4.34	6.2

In attempting to account for the formation of double eggs, the important thing is to determine how the enclosed eggs differed from those laid singly, if they did so at all. Why should they be returned to the albumen tube instead of being expelled in the normal manner?

To begin with, they were exceptionally large eggs. For six that were weighed, after being freed of adherent albumen, washed, and air-dried, the actual weights were 75.7, 69.7, 78.2, 75.7, 74.1, and 76.6 gm. Their average weight, 75 gm., was not only 5 gm. more than that of the same hen's eggs that were laid singly, but far above the normal size for the

species. In March, '43, average egg-weights were determined for all White Leghorn females of the '42 generation to which K 304 belonged. In a sample of 500 such birds, the modal class, comprising 41% of the population, laid eggs with average weights from 55 to 60 gm. and only three hens, or 0.6%, laid eggs with average weight exceeding 70 gm. Even these were only 71.5 gm. in one case, and 72.5 in the other two. It is clear, therefore, that K 304 was laying extremely large eggs and that the ones subsequently enclosed in double eggs were phenomenally large.

Since the average amount of albumen in the enclosed eggs was 4.42 gm. more than in the single ones this obviously accounted for most of the absolute difference in size of the two classes. On a percentage basis, however, this increase was only 9.6%. A relatively much greater increase, 18.2%, was found in the weight of the shell (with membrane) although the actual difference was only 0.79 gm. This indication that the enclosed eggs had thicker shells than those laid singly was confirmed by tests of the breaking strength of the shells. For the eggs laid singly, the average breaking strength was only 1.5 kg., much less than the normal figure of 4.5 kg. for eggs tested by the same method (Romanoff, '29). For the enclosed eggs, the average figure of 2.12 kg. was 41.3% higher. The measurements of shell thickness also show that shells of the enclosed eggs were thicker than those of single ones from the same hen.

INTERPRETATION

Origin

The double eggs described in this paper can be accounted for only according to the theory put forth by Davaine (1861) and supported by Parker ('06), Curtis ('16), Asmundson ('33), and others. This holds that the enclosed egg is returned from the uterus to the albumen tube, by antiperistalsis or otherwise, is again moved back to the uterus, acquiring on the way albumen, membranes, and shell, and is eventually laid as a double egg.

The alternative theory of Panum (1860), Henneguy ('11) and others, supported in recent times by Justow ('27) and Hahn ('30), contends that the egg to be enclosed remains in the uterus until overtaken by a second egg, both being then enclosed in one big shell. Justow's belief that an egg is not likely to be returned from the uterus to the albumen-tube is completely refuted by the occurrence of fully-formed eggs in the body cavity. A number of such cases are cited by Curtis ('16). The junior author once removed two eggs from the body cavity of a hen,

both complete with shells. Mr. R. F. Ball of this laboratory advises us that he has found a number of similar cases in the course of several thousand autopsies. In one of these the crushed shells of no fewer than 11 different eggs could be recognized.

In the double eggs described in this paper, clear evidence that the enclosed egg did return to the albumen tube is provided by the fact that in every case the enclosed egg and the yolk were firmly held together by the mass of dense albumen closely surrounding both. It is secreted only in the albumen tube. It is also clear that the amount of albumen enclosed in each double egg was far in excess of that induced by the stimulus of a yolk alone.

If the yolk had come down the oviduct alone it would have acquired its own coating of firm albumen and its own membranes in the isthmus, but neither of these envelopes could have enclosed any egg waiting in the uterus. This is obviously what happened on June 4th (and apparently also on May 24th) when K 304 laid a single egg with normal shell, and then, within 20 minutes, a second egg covered only by shell membranes and lacking any calcareous shell.

While the preponderance of the evidence from previously reported double eggs has confirmed the view that they arise from return of the egg to the albumen-secreting region, there has not hitherto been adduced any satisfactory explanation of the stimulus that might cause such a return. A clue to that problem is provided by the present data. It seems probable that all the eggs subsequently enclosed in double ones had been retained in the uterus for a somewhat longer time than normal. This is attested by the facts that: (1) they were distinctly larger than the eggs laid singly by the same hen; (2) they were thicker in the shell than the single ones, indicating a longer stay in the shell-forming region; i.e., the uterus, and (3) a double egg always followed a day on which no egg was laid.

It is, therefore, quite probable that, instead of being laid from 10 to 60 minutes before the next yolk was released from the ovary, as Warren and Scott ('35) found to be the usual course of events, these big eggs were still in the uterus when the infundibulum of the oviduct engulfed that yolk.

According to Warren and Scott "as soon as the ovum was entirely enclosed by the infundibulum it appeared to act as a stimulus to the entire oviduct. The anterior end of the magnum (albumen-secreting region) showed continuous serpentine contractions while other portions of the oviduct showed frequent wave-like activity. The uterus also underwent constant contractions." It does not seem improbable that under

such excitation antiperistalsis might carry an egg from the uterus back to the albumen tube.

This hypothesis is tenable only if the ovulation that normally closely follows the laying of an egg is not dependent upon the latter process. Evidence that this is so was found by Warren and Scott (loc. cit.) in the fact that experimentally-induced premature expulsion of the egg caused no corresponding acceleration of the ovulation of the next yolk. Presumably, therefore, it is not necessary that the egg in the uterus be expelled before the next yolk can be released from its follicle.

Although the explanation given above seems to the writers the most logical one so far as their series of ten double eggs is concerned, there is a question to what extent it may account for double eggs in general. From the numerous cases in the literature reviewed by Davaine (1861), Parker ('06), and Curtis ('16), it would seem that it is unusual to find in the enclosed egg a large fully-formed one. In the majority of cases it is smaller than normal (as, for example, in Curtis's specimens 11 to 16) and it frequently lacks a yolk. Such dwarf eggs are not uncommonly laid and there is no reason to suppose that they might be held unduly long in the uterus as does seem likely with the large eggs of the present series. However, it is quite probable that dwarf eggs, some formed only around little bits of albumen and others containing yolk fragments, are not formed in the same rhythmic cycle as the normal eggs, and that one of them might, therefore, easily be in the uterus when a normal yolk is ovulated. In such cases, the dwarf eggs could then be carried back to the albumen tube during the resultant "excited" stage of the oviduct described by Warren and Scott.

Orientation and shape

In all the double eggs reviewed by Parker ('06), and Curtis ('16), there was only one exception to the general rule that the pointed end of the enclosed egg is directed toward the pointed end of the enclosing egg, with the enclosed yolk, if there is one, in the blunt end of the outer egg. This was taken to indicate that the axial relationships of the enclosed egg to the oviduct are usually unaffected during its return to the albumen tube and subsequent journey back to the uterus. Since about 90% of all eggs are formed with the pointed end caudad (Olsen and Byerly, '32), the maintenance of its original orientation would bring the enclosed egg back to the uterus with the small end caudad and its succeeding yolk, if there were one, at the blunt end. Presumably, the new outer shell would then be formed with its small end also caudad.

Curtis doubted the accuracy of the observations in the one exception known to her (Pick's egg) in which the situations just described were exactly reversed, so that the enclosed egg lay in the blunt end of the enclosing egg, and the enclosed yolk in the other one. However, this same condition was present in all of the four double eggs of the present series in which larger and smaller ends could be differentiated in the big outer shell (fig. 3). In all four the yolk is in the pointed end. In two cases, nos. 7 and 9, the smaller end of the enclosed egg points toward the large end of the outer shell, one of them somewhat obliquely. It seems certain (because of the position of the free yolk) that in these two the enclosed egg was returned to the albumen tube and back up to the uterus in approximately the same orientation as that in which it was formed; i.e., small end caudad. However, when the outer shell was formed, it was bigger at the posterior (caudal) end than at the anterior one. Although this is contrary to the usual shape of single eggs, it is to be expected in any double ones in which the enclosed egg is larger than the enclosed yolk and caudad to it. This is because the shape of the shell depends upon the shape of the mass to be enclosed and is determined, as Asmundson and Jervis ('33) have shown, before the egg leaves the isthmus, where the shell membranes are laid down. Obviously, the 75-gm. egg was much larger than the single yolk that followed it. When encapsulated with firm albumen, the whole mass would then be somewhat in the shape of an egg with the larger end caudad. The mystery is that this form was evident in only four eggs rather than in all of ten.

The rarity of this type in comparison with the more common situation in which the smaller ends of both enclosed and enclosing eggs point in the same direction (caudad, during formation) with the enclosed yolk, when there is one, in the blunt end of the outer shell, is undoubtedly attributable to the fact that it is unusual to find extremely large, fully-formed eggs thus enclosed. When the enclosed egg is small, or when there is no additional yolk included, both of which types are more common, the mass around which the shell membranes of the outer shell are formed should be smaller at the posterior end because the smaller end of the enclosed egg usually lies caudad.

In nos. 4 and 6 (fig. 3), the enclosed egg has evidently been reversed end-for-end at some time after its formation and before its encapsulation along with the succeeding yolk. Otherwise, that yolk should lie next to the blunt end of the enclosed egg, as in nos. 7 and 9. Two similar cases were reported by Curtis. They were accounted for by her own evidence that, while the egg is normally formed with the smaller end

caudad, its position may be reversed by pressure in the uterus so that the larger end is extruded first. This has since been confirmed by Olsen and Byerly ('32), who found that although only 10% of the eggs examined in the uterus were formed with the large end caudad, 20 to 30% (in different breeds) were laid that way. Presumably the muscular contractions forcing the enclosed egg back to the albumen tube could occasionally cause its reversal end-for-end just as do those causing its expulsion.

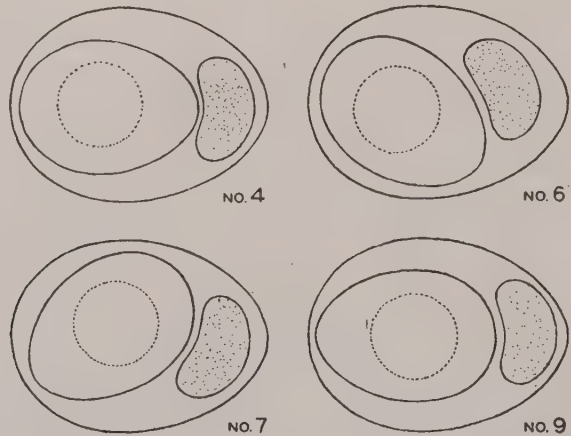


Fig. 3 Diagrammatic depiction of the four double eggs in which large and small ends could be differentiated, all drawn as they are presumed to have lain in the uterus (i.e., with the enclosed yolk cephalad) when seen from the right side of the hen. The relationships of the large and small ends of the enclosed egg to those of the outer shell and to the yolk are as observed when the double eggs were opened.

The mechanism of return

The present series of double eggs throws little light on the nature of the mechanism by which the enclosed egg is returned to the albumen tube. While most proponents of the Davaine theory have assumed that mechanism to be antiperistalsis, actual proof is lacking. The evidence reviewed by Curtis indicates that on its return from the uterus to the albumen-secreting region an egg does not acquire membranes or thick albumen. She also showed that this can hardly be attributed to exhaustion of the glands, as Hargitt ('12) proposed, and suggested (1) that the return of the egg may be too rapid for the acquisition of membranes in the isthmus, or (2) that the glands of the duct respond only to a stimulus directed caudad. None of the enclosed eggs in the present series showed any sign of membranes, nor had they any separate envelope of thick albumen. Such a condition suggests a rapid return

to the albumen-tube rather than a slow one. That an object may pass the entire length of the oviduct too rapidly to acquire albumen or membranes was shown by the laying of a bare, unruptured follicle, as reported by Hutt ('39). Such a rapid return might easily result from the contractions and waves of activity that Warren and Scott found to follow the engulfing of a yolk by the infundibulum.

It seems obvious that if that excitation of the oviduct be responsible for the return of the egg to be enclosed, it is not inevitable that the succeeding yolk will be also enclosed in the double egg. That would happen only if the completed egg were carried back till it met its successor. In other cases, if the egg subsequently enclosed were quickly carried back as far as the distal end of the albumen tube and then again passed along to the uterus, the result would be a double egg without any free yolk. This apparently is the more common type.

DISCUSSION

Although these double eggs, weighing from 170 to 193 gm. each, were phenomenally large for the species, they were not as big as the 204-gm. egg of the same type described by Henneguy ('11). The record size for eggs of the domestic fowl may be the 8-ounce eggs (227 gm.) reported by Brown ('39) from a Scottish Rhode Island Red. These were remarkable for their huge size, but also because they contained not only a complete, shelled egg but two free yolks as well.

Parker ('06) commented on the fact that the laying of large double eggs (not ordinary double-yolked eggs) was followed by the death of the hen. In the present case K 304 died on July 26th, 15 days after the last double egg, but only 7 days after the last of two soft-shelled eggs. Whether or not her death resulted from abnormalities in her egg-laying is unknown.

SUMMARY

A White Leghorn hen laid at least ten double eggs, weighing 170 to 193 gm., each with a shell and containing a complete, shelled egg, albumen, and a yolk.

Measurements and weights of the enclosed egg and its component parts, when compared with those for single eggs laid by the same hen, showed that the enclosed eggs were unusually large and had thicker shells than the eggs laid singly.

From this and other evidence, it is concluded that the egg subsequently enclosed had been retained unduly long in the uterus and that its return to the albumen tube had been caused by the excitation of

the oviduct following the engulfing of the next ovum. Later, on its way back to the uterus, the egg and the succeeding ovum acquired common envelopes of albumen, membranes and shell, the whole finally being laid as a double egg. It is suggested that the enclosure of dwarf eggs in double eggs may also result from the postovulatory excitation of the oviduct.

In four of the double eggs, blunt and pointed ends could be distinguished, and the evidence indicated that these had been formed with the larger end caudad. In two of the four, the enclosed egg had apparently been reversed end-for-end after its formation.

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MEDIAN HARELIP, CLEFT PALATE AND GLOSSAL AGENESIS

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TWO FIGURES

The problem of faulty development of the facial region has genetic, embryological, and clinical aspects. We present a case having considerable interest because of the degree of the defects and their correlation with others well removed from the facial area. The intact body and the clinical record were made available through the courtesy of the Department of Pathology of this medical school.

A female infant, 4 weeks of age, died of undetermined causes, malnourished and dehydrated (fig. 1). It had an inflammation of the pharynx which did not extend further and there was no other critical pathology discovered. A hematoma on the cranium, not connected with the meninges, showed a gas bacillus infection at autopsy but did not cause a bacteremia. The only defect that appears to serve as a cause of death was inability to swallow because of anatomical defects of the mouth.

An anatomical study revealed that there was a median harelip which did not reach the nose. Behind this (fig. 2) the premaxilla was complete and normal. The hard palate, however, formed merely a pair of ridges on the medial aspect of the upper jaw and did not meet to separate the mouth and nose. Teeth in this upper jaw and in the lower jaw were essentially normal. The soft palate was represented only by a mucosal fold on the margins of the palatal ridges with a median and two lateral teat-like projections.

Above the palate the nasal septum was complete to the premaxilla and then arched upward, leaving the nose widely open to the mouth through the primitive choanae. The nasal openings were small and the tip of the nose was flat and poorly developed. Conchae on the lateral wall were simplified and partly missing.

The lower jaw was essentially normal in bone structure, teeth, muscles, and glands though the submandibular gland was fused to the parotid. The anterior two-thirds of the tongue was missing so that the bifid posterior root projected like a stump from the floor. The

larynx seemed normal. The fat pad and facial muscles were nearly normal except that the quadratus labii superioris twisted medially, making no contact with the orbicularis oris. Emaciation of the body had not reduced the fat in the cheeks.

The lingual vein and artery were small, the vein draining into the anterior facial and the artery coming off from the external maxillary



Fig. 1 Median harelip, cleft palate and glossal agenesis.

instead of the external carotid. Otherwise vascular channels were normal. All nerves, including the hypoglossal and lingual, were normal in size and relations. The first cervical vertebra was abnormally compressed.

Development. The tongue defect goes farthest back in origin. Apparently the occipital somites contributed their share to the root of the tongue musculature and the twelfth nerve followed them down. The normal size of both fifth and twelfth nerves indicates agenesis rather than atrophy of the anterior tongue. The tuberculum impar and mandibular swellings were not sufficient evocators of muscle. The

completion of the choanae, premaxillary bar and septal fusion indicates that development here went as far as the 12-mm. stage before it failed. Todd studied the effects, on the form of the face, of defects involving one or more of the elements in this complex fusion.

The facial defects appear to have nothing in common with other anomalies. While all parts of the vascular system were normal in completing development and in the relations of parts, the heart was

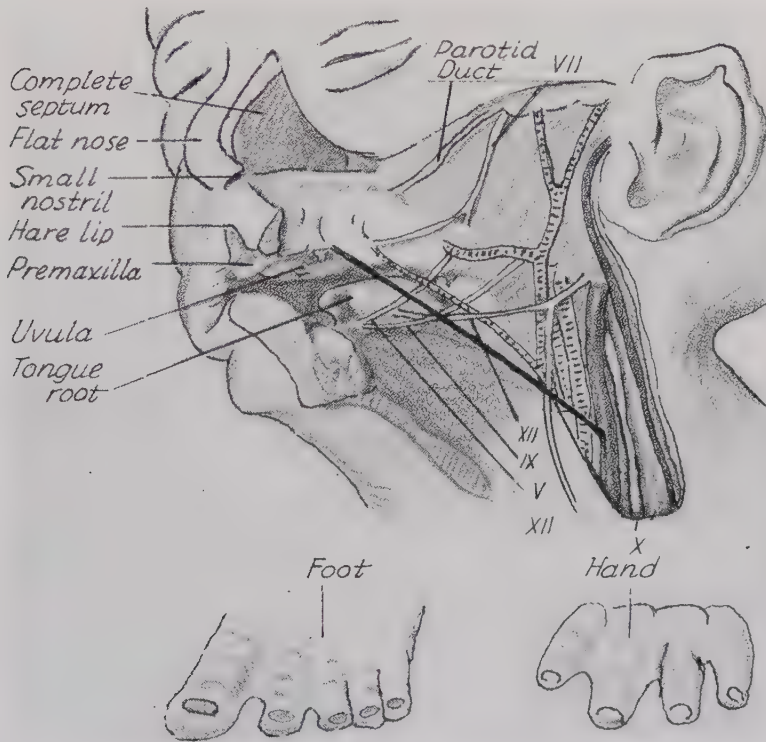


Fig. 2 Multiple anomalies in an infant.

found to be very small (20 gm.) in an infant weighing nearly 7 pounds at birth. The separation of oxygenated and venous blood was complete but the supply to the extremities was inadequate. This was correlated with short digits, having all joints intact but united by webs between all the fingers and three toes on each foot. Failure of cardiac development probably began rather late in embryonic life but before digits were well separated. A number of cases of digital defects related to vascular insufficiency have been seen by us and one was published by Sinclair and Schofield ('44). Davies ('28), had noted a correlation

between harelip and digital defects. The stillborn presented by Ashley and Richardson was more defective than this infant but the associated placental defects complicate the picture.

Genetics. The older literature cited many non-genetic factors in probable etiology. Today we are inclined more to cite genetic causes. Particular gene mechanisms are difficult to define but Murphy's study showed that for most anomalies the family incidence is high.

Anomalies of the fingers are, in some instances, associated with lethal factors so that only heterozygotes can live (Scott, '28; Haldane, '42). It is stated that webbing is in some cases an autosomal recessive, in others (Iltis) sex linked with female predominance and in one case on the Y chromosome. Bagg ('29), used x-rays on mice, producing inherited limb defects. In the present case it looks as if the digital webbing and brachydactyly were the peripheral result of defective circulation and the vascular factor may be the lethal mechanism in more defective cases. No study of a correlation of vascular deficiencies and facial or vertebral defects is known to us.

Microglossia forms 0.1% of facial defects. It is more often associated with lower jaw defect than with the upper jaw though its etiology is poorly analyzed. Median harelip is very rare. It formed about 0.47% of harelip in the series of Davis. Harelip constitutes 13% of facial anomalies and median harelip is about 3% of all harelips. For no known reason harelip occurs in three males to two females and three on the left to two on the right. It is more common in white than in colored races. Associated defects are uncommon and common etiologies are unknown. However, such associations have been used in linkage studies to indicate loci in sex chromosomes or autosomes on the assumption of separate genes for each by Schroder and Hillenbrand ('42). Mather and Philip have given both German and English data a mathematical treatment showing that Schroder's cases, published in 1931, were partly sex-linked and partly autosomal while the English group of Sanders ('33), were autosomal. In the case under consideration it is, as usual, difficult to get family history. We do know, however, that a sister of the mother of this child was born with a defective head and arm and died soon after birth. The present child is a first born.

In view of the genetic assumptions, the studies of Steiniger and Veit ('42), and Idelberger and Idelberger ('40), dealing with twin series would be of great value if they were available to us. Sangvichien found harelip and cleft palate in one of a pair of cojoined twins. In our Museum of Pathology there is a pair of full term twins joined only by the crown of the skull and facing in opposite directions. One member of

this pair has a harelip while the other is normal. With our present ignorance of developmental mechanisms the term somatic segregation adds nothing to clarity.

In general studies of anomalies we have evidence that makes genetic mechanisms particularly difficult to understand. Murphy's abundant data from Philadelphia showed that when one anomaly appeared in a family the chances of another were twenty-four times that of any average family in the community. This, of itself, would indicate a rare recessive appearing in homozygous form. Davis, however, found harelip repeated not only within families but also in near relatives with modified forms. This makes the rare recessive hypothesis very difficult to comprehend. It seems certain that these skeletal phenomena are only the external expression of syndromes the deeper and more significant parts of which are never seen nor studied. They strike us as being the result of interference between heterogeneous systems of development having slightly differing rates or terminal results and these in turn have peripheral effects along the stress lines between them. We see increasing evidence of this in the incompatible blood protein systems affecting one another across the placental barrier as its selective efficiency drops late in gestation. The Rh factor is a case in point.

SUMMARY

A 4-weeks-old infant died of undiagnosed causes. She had a rare combination of congenital defects which the family history indicates were probably hereditary in origin. The anomalies include failure of the tongue and palatal primordia to complete development, a median harelip, simplified conchae and small nostrils. Teeth and glands of both jaws were normal, nerves and blood vessels nearly normal. There was a small heart and correlated presence of brachydactyly, syndactyly, and an upper vertebral defect. A cranial hematoma was present but not obviously based on developmental defects.

Genetic and developmental etiology is discussed.

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QUANTITATIVE STUDIES ON THE BLOOD AND BONE MARROW OF NEWBORN MONGREL PUPPIES

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In a previous report (Mulligan, '41) the quantitative data on the bone marrow of thirty-five adult mongrel dogs and of four puppies were presented and a method of serial biopsy of the bone marrow of the living dog by resection of segments of the seventh through the twelfth ribs was described. Since then two other papers dealing with the bone marrow of adult dogs have been published. Van Loon and Clark ('43) performed differential counts on smears of extruded rib marrow examined immediately following the sacrifice of eight normal mongrel adult dogs. Meyer and Bloom ('43) studied the cellular composition of bone marrow obtained by needle puncture from the crest of the ilium in ten normal living dogs (eight thoroughbred, two mongrel), 1 to 11 years old. No quantitative study of either the bone marrow or the blood of newborn puppies has been found in the literature. During the past few years the blood and bone marrow of twenty-one mongrel puppies have been investigated in this laboratory. These animals were born of clinically healthy bitches pregnant at the time of reception into the animal quarters. The five litters represented included five puppies born on November 26, 1941; nine on July 17, 1942; three on November 5, 1942; one on September 15, 1943 and three on June 14, 1944. Following a lethal intraperitoneal dose of nembutal $\frac{1}{2}$ to $2\frac{1}{2}$ days after birth, 1 cc. of blood was obtained by apical intracardiac puncture between the ribs adjacent to the left side of the sternum and rendered fluid by gentle and thorough mixing with an isotonic quantity of potassium oxalate. Each animal was either in the last few respiratory movements before death or had just ceased breathing, a matter of a few seconds, when the blood sample was withdrawn. In most instances, a second sample of about 2 cc. of blood was allowed to clot to obtain serum for preparation of the marrow smears. This serum was invariably light red tinged, probably due to intravascular hemolysis, for the 2-cc. syringes and the no. 22-gauge needles, stored after cleansing in an antiseptic solution of one part 40% formaldehyde and 99 parts 95% ethyl alcohol, were thoroughly dried before use. The hemoglobin was calculated with a Dubosecq colorimeter equipped with 1-mm. thick

Newcomer glass square. To further standardize the instrument, the hemoglobin content of a sample of oxalated whole human blood was determined by the method of Van Slyke ('18) and Haldane's scale. Into each of 5, 7.5, 10, 15, and 20 cc. quantities of 1% hydrochloric acid, .01 cu. mm. of this blood was introduced, mixed, and allowed to stand for 24 hours at room temperature. By the light of the southern sky, an average of twelve readings for each sample was then taken to construct a curve, a standard for this investigation and for a study of the blood of adult mongrel dogs (Mulligan, '41). On this curve the hemoglobin could be read in grams per 100 cc. of whole blood directly from each colorimeter point. The values so obtained were 8% lower than those found by the use of Newcomer's tables (Newcomer, '19). The erythrocytes in millions and the leucocytes in thousands per cubic millimeter were counted in a Neubauer bright line counting chamber. The differential counts were made on 200 cells on slide films stained with May-Grünwald-Giemsa stain. The few damaged cells present in each smear were disregarded.

The values for the blood constituents mentioned for the thirteen male and eight female puppies of this series have been summarized in detail in table 1.

Since the level of hemoglobin, the partition of the differential count of the leucocytes, and possibly the total leucocyte count were not stabilized in the first $\frac{1}{2}$ day of life, nor for certain by $2\frac{1}{2}$ days, means and standard deviations for none of the blood constituents have been calculated pending the opportunity for serial hematopoietic studies in relation to age on puppies less than 2 months old. However, the data in table 1 may be summarized as follows insofar as ranges of the values are concerned: hemoglobin 13.0 to 23.4 gm.; erythrocytes, 4,170,000 to 6,160,000 per cubic millimeter; leucocytes (uncorrected for normoblasts present), 5,200 to 28,150 per cubic millimeter; stab neutrophils, 8.0% to 47.0%; segmented neutrophils, 31.5% to 67.0%; lymphocytes, 2.0% to 32.5%; eosinophiles, 0.0% to 5.5%; monocytes, 0.0% to 3.0%; and normoblasts, 0.5% to 14.0%. Myelocyte neutrophils were found in two counts, 0.5% and 1.0%. Metamyelocyte neutrophils were observed in thirteen counts, 0.5% to 5.0%. Basophiles were never encountered in any of the counts. The unstable hemoglobin values as compared with the relatively constant level of the erythrocytes may be the result of the release of hemoglobin from the erythrocytes into the plasma by diffusion during and after the abrupt transfer of the puppies at birth from the intrauterine environment to that of the outside world. In the first $\frac{1}{2}$ day of life, the increase in the total neutrophilic cells and

TABLE 1
Data on the peripheral blood of twenty-one newborn mongrel puppies.

NO. DOG	AGE (days)	SEX	Hb	RBC	WBC	MET N.	ST N	SEG N	LYMPHO	EOS	MONO	NORMO
P6-2	$\frac{1}{2}$	M	19.2	6.13	22650	1.5	34.5	49.5	11.0	0.5	0.0	2.5
P7-2	$\frac{1}{2}$	F	15.8	5.85	28150	4.5	47.0	31.5	9.5	3.5	1.0	3.0
P8-2	$\frac{1}{2}$	M	17.6	5.87	22800	1.0	23.5	63.5	5.0	4.5	1.0	1.5
P9-2	$\frac{1}{2}$	M	16.6	4.57	12400	1.0	26.5	60.5	8.5	1.0	0.5	2.0
P10-2	$\frac{1}{2}$	M	16.4	4.59	12250	1.5	30.0	40.0	13.0	1.0	0.5	14.0
P11-2	$\frac{1}{2}$	M	14.2	4.17	20300	3.0	30.0	53.0	8.0	1.5	1.0	3.5
P12-2	$\frac{1}{2}$	F	16.6	5.24	22100	2.0	29.0	60.0	2.0	1.0	0.0	5.0
P13-2	$\frac{1}{2}$	F	16.0	5.03	13400	5.0	26.0	60.0	7.0	0.0	0.0	2.0
P14-2	$\frac{1}{2}$	F	18.2	5.20	11050	3.0	26.0	51.5	15.5	1.5	0.0	2.5
P21-5	$\frac{1}{2}$	F	15.4	4.48	13900	..	23.0	57.5	9.5	0.0	2.5	7.5
P22-5	$\frac{1}{2}$	M	17.2	5.46	13150	..	18.0	67.0	11.5	0.0	0.0	3.5
P23-5	$\frac{1}{2}$	M	23.4	6.16	18800	0.5	25.0	63.0	5.5	0.0	0.0	6.0
P18-4	$1\frac{1}{2}$	M	19.0	5.05	11300	0.5	24.5	52.5	19.5	2.0	0.5	0.5
P1-1	2	M	14.4	4.83	10700	..	15.0	51.5	23.5	5.0	0.5	4.5
P2-1	2	M	14.6	4.65	10450	1.5	8.0	48.5	31.0	5.5	3.0	2.5
P3-1	2	M	15.2	5.62	9000	0.5	15.0	43.0	32.5	3.0	0.0	6.0
P4-1	2	F	13.0	5.60	9400	..	14.0	53.5	25.0	4.0	0.0	3.5
P5-1	2	M	15.2	4.92	5200	..	9.0	62.0	22.0	2.0	2.0	3.0
P15-3	$2\frac{1}{2}$	M	13.4	4.68	21400	..	11.0	63.5	22.0	2.0	0.5	1.0
P16-3	$2\frac{1}{2}$	F	13.0	4.26	16400	..	10.5	62.5	19.0	3.0	1.0	4.0
P17-3	$2\frac{1}{2}$	F	14.6	5.06	12550	..	16.5	62.0	18.0	1.5	0.0	2.0

Key: No. — number of; Hb — hemoglobin in grams per 100 cc. of whole blood; RBC — erythrocytes in millions per cubic millimeter; WBC — leucocytes per cubic millimeter; Meta — metamyelocyte; N — neutrophils; St — stab; Seg — segmented; Lympho — lymphocytes; Eos — eosinophiles; Mono — monocytes; Normo — normoblasts.

the shift to the left in their partition with the concomitant reduction in lymphocytes may be a reflection of lingering estrogenic material transferred across the placenta from the blood stream of the mother to that of the fetus. The papers containing the evidence that estrogens stimulate granulocytopoiesis in the dog have been quoted in a previous communication (Mulligan, Longwell, and Morrell, '43).

Slide smears of the marrow of one or more ribs were prepared with serum and histologic sections were cut from at least one rib of each animal by a technique already described (Mulligan, '41). By study of the histologic sections, the normal cellularity of the marrow of the puppies was different from that determined for the thirty-five adult mongrel dogs mentioned; namely, a ratio of 65 to 35 of marrow cells to fat tissue, for the marrow of the puppies uniformly revealed no fat tissue whatsoever, but rather consisted entirely of marrow cells.

The organs of all twenty-one puppies were anatomically normal at reasonably complete autopsy including examination of the central nervous system.

The results of the differential counts of 500 cells each on suitable smears stained with May-Grünwald-Giemsa stain have been listed for the twenty-one puppies in table 2. The data for the thirty-five adult mongrel dogs have been arranged for comparison. In contrast to the values for the blood of the puppies, the data for their bone marrow were reasonably constant, so that it was possible to calculate means and standard deviations for them. The factor, $n - 1$, was substituted for n in the usual equation, $\sigma = \sqrt{\frac{\sum X^2}{n} - (MX)^2}$, for the calculation of the sigma, σ , or standard deviation. In this formula $\sum X^2$ is the sum of the squares of the values in the series of twenty-one puppies, n is the number of animals, and $(Mx)^2$ is the square of the mean for the values. In checking the data for the thirty-five adult dogs, errors in the calculation of the sigmas for myelocyte neutrophiles and for normoblasts were discovered. The correct figures have been inserted in table 2.

In the marrow of the puppies, stem cells did not occur with significant enough frequency, actually an average of one cell per 500 cells counted, to include them in the table. Megakaryocytes were plentiful in the sections, but were too few in the smears to figure in the differential counts. Reticuloendothelial cells, plasma cells, and monocytes

were present in insignificant numbers in a count of 500 cells. Macrophages, heterophil cells (Stasney and Higgins, '37) and basophiles were not found in either smears or sections of the rib marrow. Cells having basophilic granules, which have been observed occasionally in the bone marrow of normal adult mongrel dogs, but never in the peripheral blood, have been identified as mast cells. With the technique employed, the preservation of the nucleated cells of the bone marrow of the puppies as viewed in the smears was not so good as that in the

TABLE 2

Data on the bone marrow of twenty-one newborn mongrel puppies and thirty-five adult mongrel dogs.

	Minimum	21 PUPPIES			35 ADULT DOGS	
		Maximum	Mean	Sigma	Mean	Sigma
Eosinophiles	0.0	5.2	2.4	1.50	3.7	1.49
Promyelocyte						
Neutrophiles	0.0	2.2	0.8	0.60	1.5	0.91
Myelocyte						
Neutrophiles	2.0	6.6	4.3	1.47	4.7	1.98
Metamyelocyte						
Neutrophiles	7.2	12.0	9.7	2.45	10.5	3.49
Stab						
Neutrophiles	14.8	28.4	20.6	6.27	31.0	8.32
Segmented						
Neutrophiles	0.8	6.6	3.4	1.92	3.9	2.26
Proerythroblasts	0.4	3.2	1.3	0.68	0.5	0.29
Erythroblasts	3.0	9.4	5.8	2.26	1.5	0.87
Normoblasts	33.0	56.6	45.1	12.76	38.1	11.49
Lymphocytes	1.6	6.0	3.3	1.45	1.9	1.46
Unidentified						
Cells	0.8	5.4	3.1	1.33	2.1	1.18
Myeloid/Erythroid						
Ratio	0.48	1.39	0.83	0.33	1.6	0.88

adult dogs, although the leucocytes in the peripheral blood of the puppies were as well preserved and stained as those of the adults. This is reflected in the higher percentage of unidentified cells in the marrow of the puppies noted in table 2. Damaged cells were disregarded and areas of the smear where the cells were well spread out and stained were chosen in the differential counting of the bone marrow.

By employing the formulas, $S. E._{diff.} = \sqrt{(S. E._{M_1})^2 + (S. E._{M_2})^2}$ and $S. S. = \frac{M_1 - M_2}{S. E._{diff.}}$, in which $S. E._{diff.}$ is the standard error of the

difference of the means, $(S. E._{M_1})^2$ is the square of the standard error of the first mean, $(S. E._{M_2})^2$ is the square of the standard error of the second mean, S. S. is the statistical significance, M_1 is the first mean, and M_2 is the second mean — the significant differences between the data on the bone marrow of the newborn puppies as compared with those on the bone marrow of the adult dogs were in the eosinophiles (3.2), promyelocyte neutrophils (3.5), stab neutrophils (5.2), proerythroblasts (5.0), erythroblasts (8.4), lymphocytes (3.4), and myeloid/erythroid ratio (4.7). The figures in parentheses indicate statistical significance, since they are all three standard deviations or more. The differences in the normoblasts (2.0) and the unidentified cells (2.8) are significant beyond two standard deviations. The differences in the myelocyte (0.87), metamyelocyte (1.0), and segmented (0.88) neutrophils were one or less, demonstrating no statistical significance.

SUMMARY

1. The blood and bone marrow of twenty-one newborn mongrel puppies, $\frac{1}{2}$ to $2\frac{1}{2}$ days old, were quantitatively studied.

2. Since the level of hemoglobin, the partition of the differential count of the leucocytes, and possibly the total leucocyte count were not stabilized in the first $\frac{1}{2}$ day of life, nor for certain by $2\frac{1}{2}$ days, statistical analysis of the blood constituents of newborn and very young puppies must await the gathering of data related to age for the first 2 months of canine life.

3. The figures for the bone marrow of the twenty-one mongrel puppies were reasonably constant and were compared statistically with those for thirty-five adult mongrel dogs previously reported. The most important finding was a preponderance of erythrocytopoiesis over granulocytopoiesis in the marrow of the puppies. This was reflected in the peripheral blood by the presence of 0.5% to 14% of normoblasts in a count of 200 nucleated cells.

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A METHOD FOR THE COLLECTION OF NUCLEI OF EPIDERMAL CELLS^{1 2}

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ONE PLATE (TWO FIGURES)

Research, designed to secure more facts about the structure and function of the skin, can be greatly advanced by the use of methods capable of yielding data on the chemical composition of its parts. The two chief parts of skin are epidermis, without, and dermis, within. These are different embryologically, structurally and functionally. But knowledge of their chemical properties, which would be so helpful in reaching a better understanding of their nature, has for years remained obscure. No way was known by which they could be separated and individually analyzed. Attempts to cut them apart were unsatisfactory; because the plane of firm union between the two is very uneven. The epidermis cut away seldom included epidermal projections into the dermis and often included dermal papillae, which reached out into the epidermis. Indeed, it was impossible to obtain whole epidermis without any dermis in a condition suitable for chemical analysis until the heat method of separation was introduced by Baumberger, Cowdry and Suntzeff ('42). By heating the whole skin, spread out on a hot plate maintained at 51°C. for 1 minute, the grip of the dermis is relaxed so that the entire epidermis can be stripped off as a complete sheet of tissue. Quickly taking advantage of this method of separation quantitative analyses of pure epidermis were made by Carruthers and Suntzeff ('42), and by Wicks and Suntzeff ('42).

Realizing how helpful it has been to cleanly separate whole skin into its two principal layers, it seemed worthwhile to try to devise some means of separating the epidermis itself into its several components. Impressed by the remarkable success of Bensley and Hoerr ('34) in

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obtaining mitochondria from liver substance and in collecting them en masse for chemical analysis, an attempt was made to adjust their technique of separation to the epidermis. The outlook was not promising, however, for epidermal cells are so firmly bound together, and the cornified ones contain so little water, two conditions the reverse of those obtaining in the liver.

My purpose was not to collect mitochondria, but nuclei, since modifications in the latter are unquestionably important factors in epidermal carcinogenesis, clarification of which is the major research project of the Barnard Hospital (Cowdry, '43). As part of that project it was desirable to collect masses of epidermal nuclei in a condition favorable for examination by various methods. In particular, one object was ultimately to be able to measure the uptake by these nuclei of radioactive phosphorus, as Marshak ('41) has measured that by nuclei of liver and tumor tissue, and to discover whether this property changes in the course of epidermal carcinogenesis.

Many preliminary experiments were made. An effort to squeeze out the fluid contents, together with the nuclei, of epidermis (isolated by the heat method) by means of a small Wueller press yielded only slight indications of success. Grinding of frozen and fresh epidermis in a mortar was not much more helpful. Attempts to separate out the nuclei by grinding in distilled water, 0.85% aqueous sodium chloride, and 1.5% acetic acid, all gave some free nuclei but in varying and insufficient numbers.

It was obviously important to profit by the experience of others. Consequently, a few days were spent at the University of Chicago where Drs. R. R. and S. H. Bensley made preliminary experiments in modifying their technique for use with epidermis. On returning to St. Louis these experiments were continued and other procedures were attempted until the following successful technique was developed:

1. Separate sheets of whole epidermis from dermis by the heat method (51°C.) of Baumberger, Cowdry and Suntzeff ('42).
2. Place these sheets in a Waring Blendor in sufficient 0.5% citric acid to cover the blades (about 150 cc.) and blend for 5 minutes. (The Waring Blendor can be purchased from the Waring Corporation, 1697 Broadway, New York, N. Y.)
3. Filter the resulting mixture through four layers of cheese-cloth of about 16 threads per centimeter. Upon microscopic examination the residue on the cheese-cloth will be found to consist chiefly of keratin and of keratinized cells minus their nuclei as shown in figure 1.

4. Centrifuge the filtrate at a speed of 1200–1500 R.P.M. for 15 minutes. The material thrown down will be found, when examined microscopically, to consist almost wholly of nuclei which appear undamaged. They are illustrated in figure 2.

It is quite possible that other epidermal fractions, in addition to the keratin and nuclei, can be collected by appropriate washing and centrifugation. The technique works for human epidermis as well as for mouse epidermis. From negro epidermis melanin can readily be separated out.

The nuclei thus collected from mouse epidermis are somewhat distorted when they are smeared on a slide dehydrated and stained as indicated in figure 2. When, on the contrary, the emulsion of nuclei is examined microscopically, unstained, by direct illumination, their form is seen to have been surprisingly little changed by the rather drastic treatment to which they have been subjected.

The utility of this technique is of course limited. But careful study of such preparations of pure epidermal nuclei has already shown that changes in size take place during carcinogenesis which to some extent parallel those already reported by Cowdry and Paletta ('41) from observations made on nuclei in sectioned material. It is a definite advantage to be able to examine whole nuclei, and great numbers of them so that the range in variation can be established. These determinations of nuclear size and shape are being prepared for publication. But the nuclei isolated in this fashion have been exposed to dilute citric acid. Their composition may thereby have been altered so that complicating factors must be considered in chemical and physical studies of masses of nuclei. These disturbing factors do not operate in the examination of whole epidermis which is quickly separated by the heat method with the loss of only a small amount of water by evaporation, and which has been shown to be still at least partly alive, because it continues to consume oxygen.

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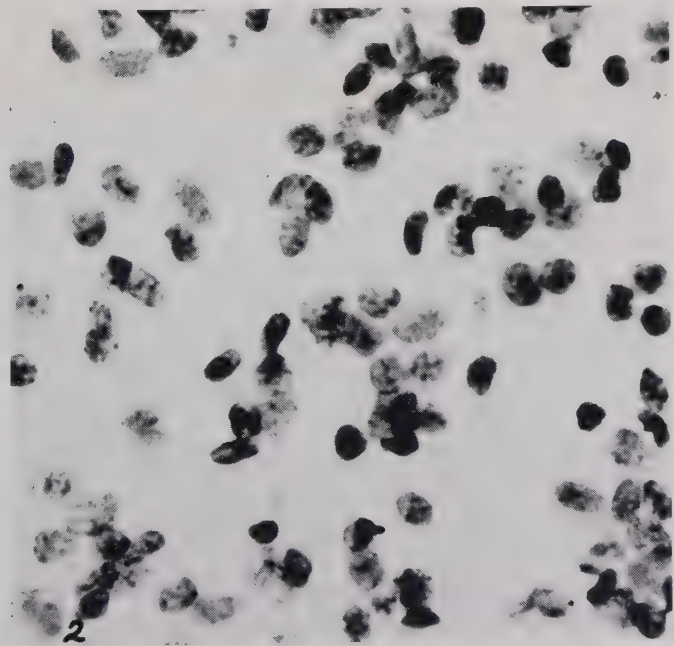
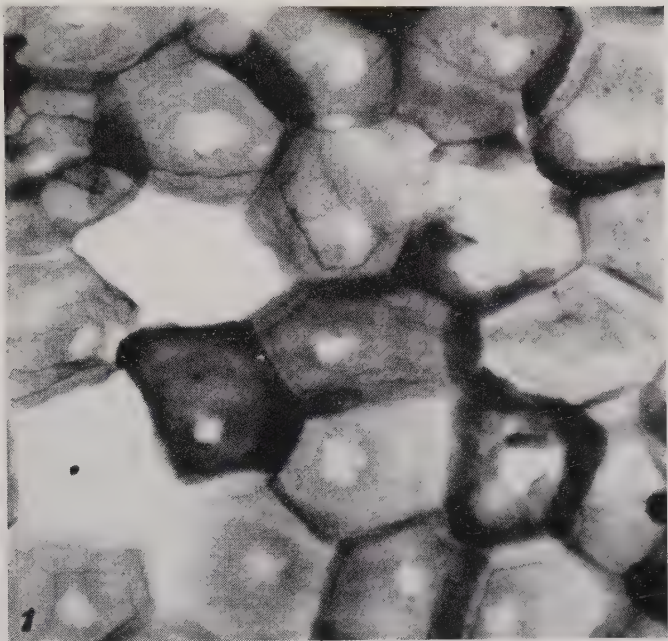
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PLATE 1

EXPLANATION OF FIGURES

- 1 Photomicrograph of whole mount of residue, showing keratinized cells minus their nuclei. Human skin, preparation stained with Harrison's hematoxylin and eosin. $\times 540$.
- 2 Photomicrograph of nuclei obtained by method described in the text. Normal mouse skin, smear preparation stained with Harrison's hematoxylin and eosin. $\times 770$.



RATE OF REPLACEMENT OF THE SURFACE EPITHELIAL CELLS OF THE GASTRIC MUCOSA

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TWO PLATES (ELEVEN FIGURES)

Gastric mucosa which has been exposed to alcohol of high or moderate concentrations of ethyl alcohol for 5 minutes or to 1% acetic acid for $\frac{1}{2}$ hour produces large amounts of opaque, alkaline mucus, throughout which innumerable intact gastric epithelial cells are suspended (Grant, '42, '43). In a brief report of histological observations made in a few of the early experiments Grant ('43) stated that the process by which these cells were replaced was evident within an hour or 2 following their loss. Additional experiments have confirmed that the speed of the replacement process is of the order found in the first cases and is more rapid than the few references to this process found in the literature would suggest. The results of this work will be described in this paper.

The regeneration of the gastric epithelium has been mentioned by a few investigators who were interested primarily from a pathological point of view in the regeneration of all of the mucosal elements following deep lesions analogous to chronic ulcers or following other types of experimental damage. Griffine and Vassali (1888) studied at intervals of 1 to 55 days the regeneration of the dog's fundic mucosa from which pieces had been taken. Their reference to the rate of replacement of the surface epithelial cells is limited to the rate at which flat epithelial cells covered the spaces between the remnants of glands at the edges of the lesions where they reported it to be 2 to 3 mm. in 4 to 5 days. Where the glands had to be completely regenerated they state only that new epithelium was seen in 3 to 5 days; that in 8 days the cells were cylindrical in shape; and "the whole surface of a large lesion was covered in 8 to 10 days." Poggi (1888) in the course of a study of the healing of mucosa of dogs after different types of suture, observed that the repair process in the surface at the edges of the wounds took 7 to 16 days but here too the glandular tissue in the vicinity had been destroyed. Carnot ('26) reported that in the dog's

mucosa lesions 1 to 2 cm. in diameter after the initial retraction, were finally covered over in 20 days with new epithelium and that this rate was doubled after embryonic extracts had been given. Caylor ('26) reported that lesions of the chronic perforating type showed flattened epithelial cells at the edges of the lesions extending over the denuded area without referring to the rate. Ferguson ('28) reported 2 mm. per week to be the rate at which surface cells from the margin extended to the center of deep gastric mucosal lesions in the dog.

In all of these cases the conditions of the experiments differed from those to be described in that the replacement of the epithelium followed deep lesions rather than loss of epithelial cells alone.

METHODS

Cats which had fasted for 24 hours were anaesthetized with chloralose-urethane given intravenously with the aid of a little ether. The corpus of the stomach was separated from the pyloric part without interfering with the blood supply, and the oesophagus was corked. The control piece of mucosa for histological examination was taken from the edge of the opening in the greater curvature just before a glass tube 1 inch in diameter was tied in. Through this tube which was uncorked only when necessary, 15 cc. to 20 cc. of 50% to 60% ethyl alcohol or 1% acetic acid were introduced and drained off in 5 minutes or $\frac{1}{2}$ hour respectively. Ten to 18 minutes after removal of the alcohol or acetic acid when it was thought that the shedding of mucus and cells would be taking place at a rapid rate, a second piece of mucosa was taken from the greater curvature. The gap in the mucosa was closed with a couple of stitches and the tube which had had to be carefully removed, was replaced. Finally before the animal was killed 1 to 5 $\frac{3}{4}$ hours later, two pieces of mucosa were taken. The mucosa samples, each about 1 sq. cm. in size, were always immersed in the mercuric-chloride-formalin fixative within 5 minutes from the time the boundry cuts had been made. Hematoxylin and eosin stains were used. Of the total of twelve experiments, the epithelial cell loss was produced by 1% acetic acid in five by 60% alcohol in another five and by 50% alcohol in two.

OBSERVATIONS

Appearances typical of the mucosa at the three stages of the experiment, i.e., during (1) control, (2) shedding, (3) recovery periods, are shown in the photomicrographs in figures 1 to 11.

In the normal resting stomach of the controls (figs. 1, 4, 7, 9) the picture was that of normal gastric mucosa. The foveolae were compara-

tively deep and numerous. At the bases of the foveolae the epithelial cells were lower in height in comparison with those at the surface. The glands were tightly packed as in figures 1 and 4 or less tightly as in figures 7 and 9.

During the shedding period (figs. 2 and 5) the most outstanding features were the thick coat of mucus containing the epithelial cells, and changes in the foveolar and neck regions. The foveolae were reduced in numbers per unit of surface in comparison with the controls and were diminished in depth, in some cases to the extent of being represented only by clusters of the basal cells at the surface. Gaps in the necks were also characteristic of this stage. While signs of shedding were never seen in the mucosa of the controls, nor in that taken during the recovery stage, it must be pointed out that the degree of shedding was not uniform in mucosa taken during the shedding period, some areas appearing almost denuded of epithelium and foveolae while other areas showed only a reduction in depth of the latter and a thinning of the surface cells.

These variations in the shedding period samples were reflected in the appearances of the mucosa during recovery, when variations in the degree to which the replacement had advanced in one and the same sample were seen. Areas which had apparently been denuded were covered with new flat epithelium between widely separated and shallow pits. Figure 11 ($2\frac{1}{2}$ hours after 50% alcohol) illustrates this stage. Figure 10 (1 hour after 1% acetic acid) is an example of an area where the shedding was apparently less extensive and the foveolae were not obliterated. Here the new surface cells can be seen to have spread some distance from the edges of the foveolae in bridging the gaps in the surface. It may be predicted that within another hour or 2 the surface would have been completely covered with newly-forming epithelium. In figure 8 ($4\frac{1}{2}$ hours after 60% alcohol) is seen an example of an area where new foveolae are appearing in numbers and depth comparable to the controls. However the newly-developing cells of the crypt linings and of the surface can clearly be seen to differ from the typical appearance of those in the controls (fig. 7). In figures 3 and 6 ($5\frac{3}{4}$ and $4\frac{3}{4}$ hours respectively after removal of 60% alcohol) the degree of regeneration is intermediate between that seen in figure 11 ($2\frac{1}{2}$ hours after 50% alcohol and figure 8 ($4\frac{1}{2}$ hours after 60% alcohol).

The rate of the replacement process has been calculated roughly on the basis of distances from the foveolar edges the new cells are found in the early stages e.g. in figure 10. Where the surface between two foveolae is completely covered it is assumed that each foveolae has

been responsible for one-half the distance covered. On the basis of these rough estimations the distances were covered in some of these experiments at the rate of 0.2 mm. to 0.4 mm. in 1 hour.

The conclusion that the mucosa was in an essentially normal state under our conditions was based on its macroscopic and microscopic appearances throughout control experiments. However the extent of shedding and the rate of replacement under ordinary conditions of digestion may differ in degree from what they have been found to be in the anaesthetized animal, the loss of the cells being either more or less extensive, and the rate of replacement either faster or slower.

DISCUSSION

The replacement of surface epithelial cells of the gastric mucosa is of interest not only from pathological but also from physiological aspects. While earlier investigators, as mentioned in the introduction, have made observations on the replacement of these cells following deep lesions of pathological dimensions involving not only the surface cells but also those underlying the surface, the replacement in the experiments reported here followed loss of the epithelial cells alone.

The agents which caused the epithelial cells alone to be shed may be considered to be within the range of substances to which the human stomach is frequently, if not commonly, as in the case of the alcoholic addict, exposed. Berry ('41) reports that in 100 alcoholics, 2 to 3 pints of whisky per day or $\frac{1}{2}$ gal. of wine or 1 gal. of beer were consumed. Gray ('43) reports for a group of alcoholic addicts 24 to 66 years of age, the consumption of 1 to 6 pints of alcoholic beverage per day for 3 to 52 years (average 2.8 pints per day), the alcoholic content of which varied from 20% to 90%. Vomiting of large amounts of opaque mucus, it is generally recognized, may follow the excess consumption of alcohol. Presence of "desquamated" epithelial cells in this mucus has been recognized. Judging from the extent of epithelial cell loss caused by 50% to 60% alcohol in contact with the mucosa for 5 minutes, as observed in the experiments reported here, and from the extensive cell shedding caused by concentrations of alcohol at least as low as 20% to 30% (Grant, '44), the epithelial cell loss in the alcoholic cases described above must have been very extensive. Under these conditions a rapid replacement process would be essential for keeping the mucosa in a properly functioning state, and the failure of replacement to keep up with loss could explain the gastric disturbances which were present in a certain percentage of these cases and have been commonly described in the clinical literature dealing with this type of case. Bockus ('43)

states that "gastric symptoms are not peculiar to the chronic alcoholic but may occur also in those who are in the habit of drinking concentrated spirits in small quantities each day at a time when the stomach is empty" and mentions the symptomatic relief, so commonly recognized, which follows total abstinence from alcohol and the institution of a bland diet. These would be the conditions which would prevent cell loss from outstripping cell replacement. Where these conditions were not met, i.e., where cell loss would outstrip replacement, the buffering (both chemical and mechanical) function of the epithelial cell would be lost and the underlying gland cells would become exposed to damaging factors which would interfere in turn with their functions; this leading eventually to the manifestation of gastric symptoms. That the loss and replacement is also of interest from a physiological point of view is suggested by the results recently reported (Grant, '44) on the extent of gastric epithelial cell loss after food substances have been in contact with the mucosa.

The much more rapid rate of replacement of the surface cells, as compared with the rate observed by Ferguson ('28) and others when the mucosal cells of all types were being simultaneously regenerated following deep lesions, may be explained by the differences in the numbers of potential replacing cells under the different experimental conditions—the replacement in Ferguson's cases having to depend on the cells from the glands or crypts at the edges of the deep lesions, while in my cases the epithelial cells could be rapidly made up from the underlying glands. The exact source of these replacing cells has not been established but that they come from the regions at the bases of the crypts may be inferred from the work of Bizzozero (1893).

SUMMARY AND CONCLUSIONS

The rate of replacement of the epithelial cells of the gastric mucosa has been studied in the cat under chloralose-urethane anaesthesia. Under these conditions the mucosa appears macroscopically and microscopically to remain in an essentially normal state over the experimental period.

The cell loss, which was caused by exposure of the mucosa to 50%–60% ethyl alcohol or to 1% acetic acid for 5 minutes or $\frac{1}{2}$ hour respectively, varied in extent from a complete denudation of epithelium with almost total obliteration of the foveolae in some areas, to merely a reduction in the depth of the foveolae with a stripping or thinning of the surface cells in other areas.

These differences in the degree of shedding were reflected variably in the extent to which replacement had progressed in the recovery period of 1 to 5½ hours following removal of the alcohol or acetic acid. In the earliest stage new epithelium bridged the gaps in the surface between widely separated and almost obliterated crypts; in the most advanced, a covering of rounded or low cylindrical cells could be seen forming a new epithelium for surface and for foveolae, and the foveolae were approaching, in depth and numbers, their appearances in control mucosa.

It has been concluded that the gastric mucosa possesses the fundamental property of replacing within a few hours epithelial cells which have been shed as a result of exposure of the mucosa to substances which do not damage the underlying gland cells. The possible significance of this is discussed briefly from pathological and physiological points of view.

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PLATES

PLATE 1

EXPLANATION OF FIGURES

Gastric mucosa of 24-hour fasted cat under chloralose-urethane anaesthesia.

1-3 Cat A $\times 120$.

1 Control mucosa for 2 and 3. Normal appearance of mucosa.

2 Appearance during the shedding period, 12 minutes after removal of 60% alcohol, when surface epithelial cells are being shed in a thick coat of mucus. Other characteristics which can be seen at this stage are the gaps in the neck regions of the glands and the shallow or almost obliterated foveolae.

3 Appearance during the recovery period, 5 $\frac{1}{4}$ hours after removal of the alcohol. The regenerating epithelium can be seen.

4-6 Cat B $\times 120$

4 Control.

5 Epithelial cells being shed in mucus 16 minutes after removal of 60% alcohol.

6 During recovery period 4 $\frac{3}{4}$ hours after removal of alcohol regenerating epithelium can be clearly seen.

7-8 Cat C $\times 300$

7 Control.

8 Regenerating epithelium 4 $\frac{1}{2}$ hours after removal of 60% alcohol. In this case the newly-forming foveolae can be seen in outline. They have reached a depth comparable to that of the control foveolae but the developing epithelial cells of the surface and crypts differ in shape and in the position of the nuclei from the fully developed epithelial cells of the control.

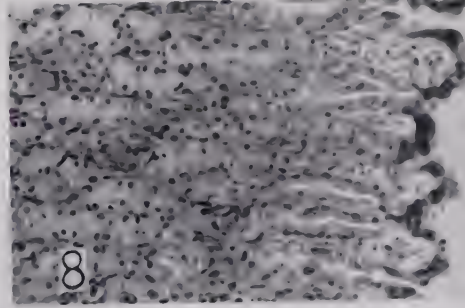
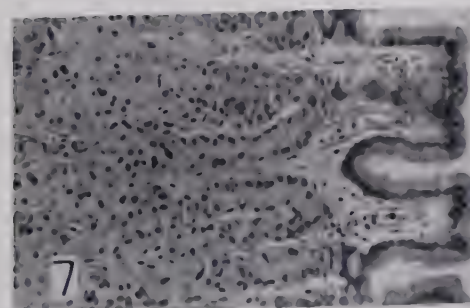
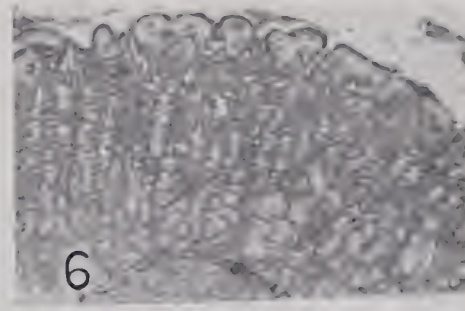
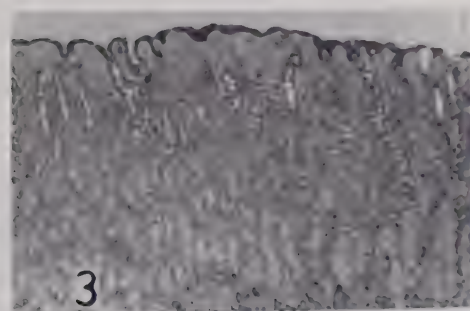
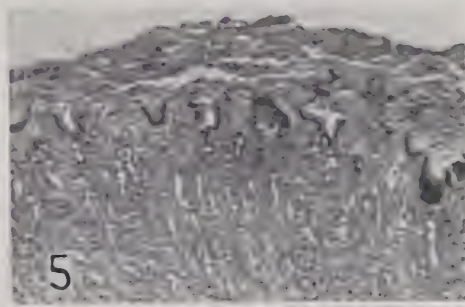
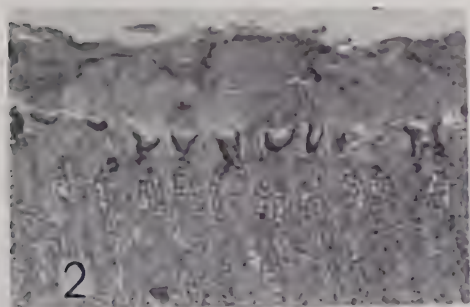
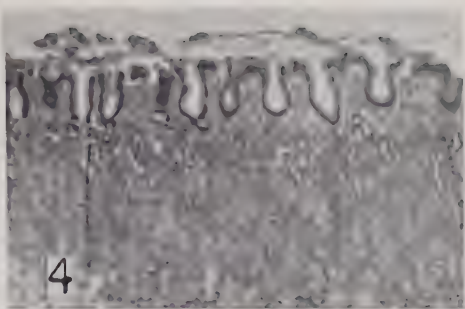
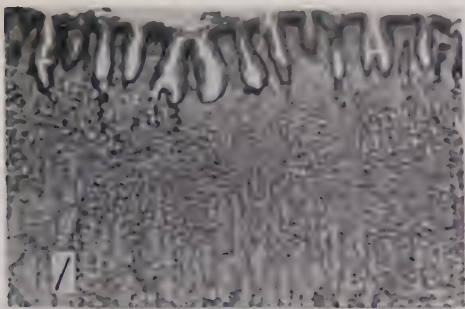


PLATE 2

EXPLANATION OF FIGURES

Gastric mucosa of 24-fasted cat under chloralose-urethane anaesthesia.

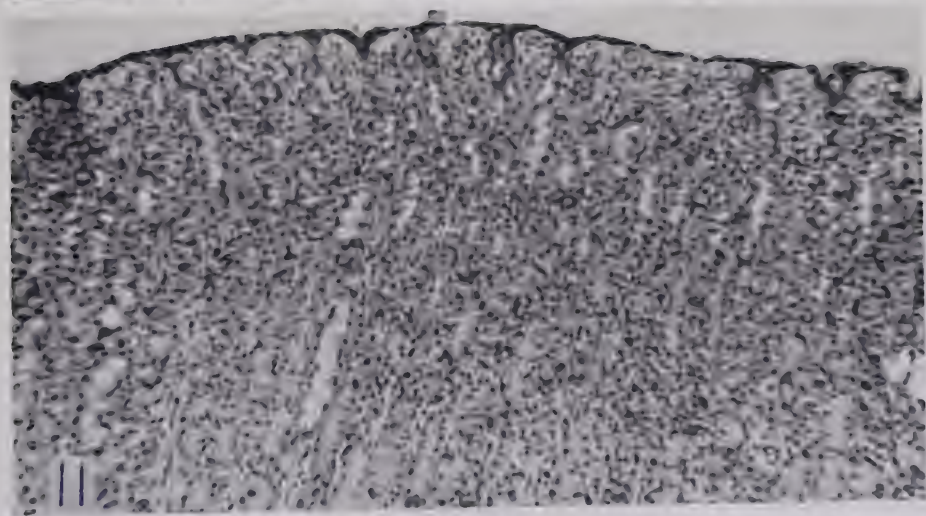
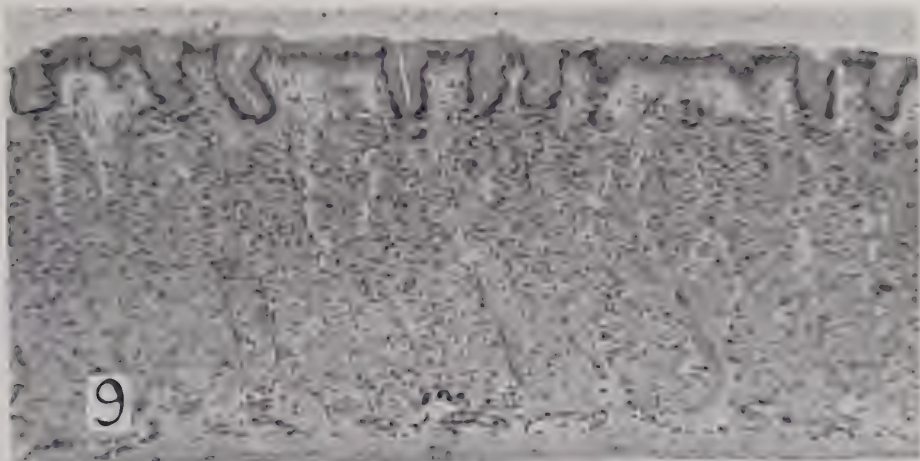
9-10 Cat D $\times 200$.

9 Control.

10 Recovery of epithelium 1 hour after removal of 1% acetic acid. New epithelium is bridging the gaps between foveolae, which in this case appear not to have been reduced or obliterated to the extent seen in some of the other samples of mucosa.

11 Cat E $\times 200$.

11 Regenerating epithelium $2\frac{1}{2}$ hours after 50% alcohol. In this sample the surface was apparently denuded and the majority of foveolae obliterated but new flat epithelium has covered the whole area.



THE RESPONSE OF THE PANCREATIC ISLANDS OF THE FROG (*RANA PIPIENS*) TO ALLOXAN

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ONE PLATE (FOUR FIGURES)

In 1943, Dunn, Sheehan and McLetchie demonstrated that injections of alloxan into the rabbit produced a necrosis of the central cells of the pancreatic islands, leaving only a ring or crescent of living cells at the periphery. Following these injections there was an initial rise in blood sugar, succeeded by a severe and usually fatal hypoglycemia. Since 1943 there have been many studies on the effect of alloxan on the pancreas and its ability to produce eventually a diabetic state due to the selective injury or destruction of the beta cells of the islands of Langerhans. (See Joslin, '44, and Bailey, Bailey and Hagan, '44, for recent reviews of the literature.) Observations have been made on several mammals, rats, guinea pigs, cats and dogs, as well as on the rabbit. No other vertebrates, lower than the mammals, with the exception of the pigeon² (Goldner and Gomori, '43) appear to have been studied. All animals investigated have been found to be sensitive to alloxan, but in varying degrees.

The primary object of the present study of the frog was to determine the effects of alloxan on the pancreas of a cold-blooded vertebrate. However, it has also been possible to add some information regarding the cellular composition of the pancreatic islands since the selective destruction of one cellular component immediately identified it as the homolog of the beta component of the mammalian island. Thus we have a confirmation by experimental means of an interpretation previously made on the basis of selective and differential staining. There was also a hope that the lower metabolic rate of Amphibia might permit a more detailed analysis of the degenerative changes in the beta cells. The process is very rapid in the warm-blooded animals.

¹ This study was carried out under the direction of Prof. Alden B. Dawson and was presented as a senior thesis in partial fulfillment of the requirements for the S. B. degree, with high honors in Biochemistry, Harvard College, 1944.

² Preliminary observations on the chick indicate that it is relatively insensitive to alloxan. Doses as large as 600 to 800 mg. per kilogram of body weight were necessary to produce results comparable to those in the frog after receiving doses of from 150 to 220 mg. per kilogram.

MATERIALS AND METHODS

Adult frogs freshly shipped from Vermont were used and animals of relatively uniform size were selected for experimentation. In a preliminary survey numerous frogs were injected with different amounts of alloxan to determine their range of sensitivity to the drug. Doses of freshly dissolved alloxan, ranging from 50 mg. per kilogram, to 1000 mg. per kilogram, of body weight and prepared as a 5% solution in distilled water, were injected into the dorsal lymph sac. Periods of survival or symptoms of injury were recorded and plotted against dosage per kilogram of body weight. Even under uniform conditions there was considerable variation in the response of individual animals to the same dosage.

However, from these data it was possible to select a so-called minimum effective dose, the lowest dose that produced death. This was found to be within the range of 150 to 220 mg. per kilogram of body weight and permitted survival of the animal for a period of 18 to 30 hours and was capable of inducing degenerative changes in the beta cells. Unfortunately it was not possible to produce irreversible injury to the beta cells and have the frogs survive for any great period of time so that an experimental diabetic condition of any duration was not obtained. Doses of lesser strength were usually ineffective and did not cause obvious changes in the pancreatic islets or kill the animals. It should be noted here that ineffective single doses were cumulative when the period between the injections was as short as 8 hours; with longer intervals there was apparently elimination of the drug and the cumulative effect was not obtained. The pancreas of these animals was not studied. Higher doses of alloxan, 300 to 500 mg. per kilogram of body weight, produced death within 4 to 10 hours; while extremely high doses, 700 to 1000 mg. per kilogram, induced almost immediate prostration of the animals, followed by death within less than 2 hours.

The pancreatic tissue was fixed in both Helly's and Bouin's fluids. At first Heidenhain's azan modification of Mallory's triple stain was routinely used after fixation in Helly's fluid (Bloom, '31; Thomas, '37) and adapted according to the procedure of De Robertis and Primavesi ('39); i.e., reduction of time of exposure to the 0.2% azocarmine solution to 15 to 20 minutes and shortening of the period in the orange G-anilin blue mixture to 1 hour. Also, in the early work, Gomori's chrome hematoxylin-phloxin method (Gomori, '41) was only used following Bouin's fixation but it was later discovered that Gomori's method was equally differential in its staining effects following Helly fixation and the general histological picture was improved.

Blood sugar determinations were made after the method of Folin and Malmos. Blood was obtained from the frog by the following method. The animal was pithed and the pericardial region exposed. A slit was then made in the truncus arteriosus and a small cannula inserted. The heart was allowed to pump blood into the cannula until sufficient had accumulated for a determination. A crystal of sodium citrate was introduced to delay clotting.

THE NORMAL PANCREATIC ISLAND

Although the structure of the pancreatic islands has been studied rather extensively in amphibians, it is only recently that the cellular components have been identified with those of mammals by the use of similar methods of selective staining. As early as 1899 Diamare successfully differentiated two types of cells in *Triton cristatus* and *Bufo viridis*. These findings were confirmed by Fischer ('12) in both *Triton* and *Rana fusca*. However, Saguchi ('20) distinguished five types of cells in *Rana temporaria*, primarily on the basis of minute cytological detail, although he did not ignore the problem of specific granulation.

More recently Kolossov ('27) described types A and B in *Triton* but felt that only type B was functional and that the A cell was probably a transitional stage between the acinar cell and the type B cell. Later Hirata ('34) identified a fuchsinophile cell in *Rana japonica* as identical with the A cell of Bensley and A, B, and C cells of Saguchi.

Janes ('38) distinguished two types of island cells in *Rana clamitans*, *catesbiana*, *sylvatica* and *Hyla versicolor*. He designated them as red and blue types following azur-eosin staining but did not relate them to the A and B types previously described. There is no doubt from his description but that the red cell is identical with the alpha cell. "The red cell was occasionally found isolated along the ductules or distributed among the acini, but more often was located on the periphery of the larger islands" (p. 379).

Apparently De Robertis and Primavesi ('39) were the first to apply successfully the Heidenhain azan method to amphibian (*Bufo arenarum*) islet tissue. They adapted the method of Bloom ('31) and Thomas ('37) and were able to demonstrate clearly a deep red cell (alpha type) selectively stained with azocarmine and an orange-colored cell (beta type) stained with orange G but were not able to distinguish either the clear cell of Bensley or the D cell whose granules in other classes of vertebrates are selectively stained with anilin blue. De Robertis and Primavesi also report an atypical cell which they interpreted as a beta cell in process of atrophy.

The normal frog pancreas is loosely organized and the islet tissue is not sharply segregated morphologically from the acinar tissue so that islet tissue is recognized only with difficulty in the absence of differential staining. There is some evidence of a capsule about the islands but it frequently merges indistinguishably with the framework of the exocrine tissue.

When Heidenhain's azan method is employed, two, but only two, clearly distinct cell types are found; peripherally located cells, which occur in irregular blocks with fine, densely packed granules stained an intense red with azocarmine and more central cells arranged in cords whose granules react with orange G. These seem identical with the alpha and beta cells of mammals which possess corresponding tinctural properties. There are apparently no delta cells since this method has always been found adequate for their demonstration (Bloom, '31; Thomas, '37, '40 and '42). With Gomori's chrome hematoxylin-phloxin technique devised for mammalian islets, the alpha cells have a uniform, bright pink color while the beta cells are shown with purple-blue granules on a pink cytoplasmic background. The beta cells are much more readily recognized in the Gomori preparations and the granules are clearly distinguished from the cytoplasm. Accordingly it is the method of choice since the orange G in Heidenhain's method does not permit such a contrast between granules and cytoplasm.

Unlike the compact island of *Bufo arenarum* (De Robertis and Primavesi, '39) the islands of *Rana pipiens* are loosely organized. The beta cells are arranged in definite cords which branch or anastomose at rather obtuse angles to form irregular patterns such as incomplete figure eights. This meshwork of cords may be followed for considerable distances among the acini and are usually accompanied by large conspicuous capillaries. The beta cells are usually greatly elongated and generally oriented at right angles to the long axis of the cord. Thus both ends frequently border on capillaries and striking bipolar accumulations of granules are present (fig. 1).

The alpha cells are densely packed with extremely fine granules which are resolved only with difficulty under optimal microscopic conditions. The cells are roughly rectangular to polyhedral in outline and usually occur in irregular clumps; sometimes separated from the beta cords by a capillary space but frequently interpolated along the cords. Isolated cells also occur among the acini and occasional cells may be seen wedged into the epithelium of the smaller pancreatic ducts. In general they tend to be peripheral to the beta tissue.

THE ISLANDS OF EXPERIMENTAL ANIMALS

The islands of the pancreas of animals which died within 2 hours after receiving single, relatively massive doses (700 to 1000 mg. per kilogram body weight) showed no changes from those of the normal control animals. However, the blood sugar concentrations, although variable, were always high. In the period from $\frac{1}{2}$ to 3 hours after injection, blood sugar concentrations were found to range from 90 to 150 mg. %. This is striking contrast to estimations made in normal frogs, which yielded values of 65 to 85 mg. % (average 74 mg. %). These figures are in close agreement with those of Welsh ('43) who obtained values of 79 mg. %.

In the second group of frogs, receiving doses of alloxan from 300 to 500 mg. per kilogram of body weight, death did not occur until 4 to 10 hours after the injection. Cytological changes in the pancreas of these animals were not pronounced. The acinar tissue and the alpha cells were normal although in a few instances the alpha nuclei appeared hyperchromatic. However, the structure of the beta cords is frequently impaired (fig. 2). The beta cells may show loss of their typical columnar form, become rounded and tend to be clumped into irregular masses. The cytoplasm appears more scanty but the nuclear patterns are well preserved, although many nuclei are rounded rather than oval in outline. The granulation of the beta cells is little changed. There is possibly some reduction in granulation or at least that appearance is produced by the tendency of the granules to be aggregated or even coalesced into larger masses. The capillaries are greatly dilated even in islands in which no cytological evidences of injury can be observed. Average blood sugar concentrations for animals dying in this period are generally lower than normal, falling within a range of 10 to 60 mg. %. The wide range of values is probably due to the fact that some animals were examined before the initial hyperglycemia had worn off.

The most complete picture of progressive injury to the beta cells is obtained from the third group of frogs which died from 18 to 30 hours after receiving doses of alloxan, ranging from 150 to 220 mg. per kilogram of body weight. Although the acinar tissue and alpha cells still appear unharmed, the beta cells always show definite evidences of injury (figs. 3 and 4).

The cytoplasm of the beta cells at the terminal stages no longer contains granules. With Gomori's method their cytoplasm appears light pink and the purple-blue color of the granules is entirely absent. After azan staining the cytoplasm is either almost colorless or takes on the light blue coloration of collagenous connective tissue. In most instances

the cytoplasm of the beta cells is greatly reduced and highly vacuolated, frequently presenting a foamy appearance. The disorganization of the beta tissue and vacuolation of the cells is reminiscent of the condition described by Kolossov ('27) after long periods of daily injections of glucose into Triton. The vacuolation appears to follow and not accompany the loss of the granules, although the granular clumping or fusion already noted may not be entirely unrelated to the subsequent vacuolation. In a few instances, probably representative of more advanced injury, the vacuolation is not present and the cytoplasm is greatly reduced or almost absent. The nuclei seem to be surrounded by thin rims of cytoplasm but the whole cell mass is so compacted that cell outlines cannot be distinguished. However, the nuclei of the beta cells usually retain their chromatin patterns and appear almost normal although rounded and slightly swollen. Occasionally nuclear pycnosis and complete disintegration of the cytoplasm are observed.

Islet architecture is also greatly modified and in most cases the characteristic beta cords are interrupted and transformed into irregular compact masses. The capillaries are either greatly reduced in size and complexity or completely absent. This reduction in blood supply may indirectly affect the alpha cells which sometimes show varying degrees of nuclear pycnosis.

At times it appeared as if there was a surplus of alpha cells but it is believed that this appearance of an increase in their number is due to a reduction in the volume of the long beta cords so as to give the impression of an abnormal number of alpha cells. The number and distribution of alpha cells is highly variable in the normal frog pancreas and it is difficult to assess the situation in individual islands. In *Bufo arenarum* De Robertis and Primavesi ('39) found the proportion of the two types of cells to be 20 to 30% alpha cells to 70 to 80% beta cells. In *Rana pipiens* the proportion of alpha cells would not appear to be so high.

One of the remarkable features of this destructive process in the pancreatic islands is the absence of any cellular reaction at or near the site of cellular injury. There is no migration of macrophages or infiltration of motile hemal elements. This absence of any cellular reaction has also been noted as characteristic of comparable lesions in the mammal pancreas (Bailey, Bailey and Hagan, '44).

Blood sugar concentrations could not be ascertained at the terminal stages of the frogs dying 18 to 30 hours after injection. This was due to the impairment of heart function when the animal became comatose and the difficulty of obtaining blood samples undiluted by body fluids.

One animal which was pithed 30 hours after injection, and before it had become comatose, had a blood sugar concentration of 150 mg. % but it was not possible to demonstrate that animals of this group generally die with extremely high blood sugar concentrations. However, the symptoms of death closely resembled those of diabetic coma and the convulsions which symbolized the earlier hypoglycemic death were absent.

DISCUSSION

The ability of doses of alloxan, comparable in magnitude to those effective in mammals, to produce injury to the beta cells of the pancreatic islands in a cold-blooded vertebrate, such as a frog, is demonstrated. It has also been shown that a relationship exists between the dosage, period of survival and the cytological picture of the pancreas.

It is to be immediately noted that the injurious effects on the beta cells do not become evident as early in the frog as in mammals and also that the necrotic process is not so complete. It is unfortunate that the dosage of alloxan sufficient to produce a satisfactory cytological end-point in the pancreas was not compatible with the survival of the animal. Remedial measures found of value in mammals did not prove helpful. Accordingly it was not possible to determine if the beta cells, apparently irreversibly injured, were capable of recovery.

In mammals morphological evidences of beta cell injury occur very early; 5 minutes after subcutaneous injections of alloxan in the rat (Hughes, Ware and Young, '44), and in the same period in the rabbit after the end of an intravenous injection of 200 mg. per kilogram dose given over a period of 10 minutes (Bailey, Bailey and Hagan, '44). In the latter case degranulation, nuclear pycnosis and early cytolysis of beta cells with a general distortion of the architecture of the islands were present at the end of 2 hours. At the end of 6 hours the mammalian pancreas frequently shows as great injury as occurs in the frog in from 18 to 30 hours after injection. The response of the islets appears to differ in two respects. The highly vacuolated condition of the cytoplasm so characteristic of the injured beta cells of the frog has not been described in mammals and the evidences of nuclear injury are much more obvious in mammals. Both show ultimately a great reduction of cytoplasmic volume with the apparent loss of cell boundaries and the appearance of cellular coalescence.

In frogs receiving the highest dosage the early death may be attributed in part to a severe acidosis due to the introduction of large amounts of alloxan into the body fluids, since alloxan, in aqueous so-

lution, behaves as a weak acid. The accompanying high concentrations of blood sugar, if we adopt the interpretation applied to mammals, would result from adrenal activity (Hard and Carr, '44). The hypoglycemia of the second group receiving lesser doses is probably due to the slow release of insulin from the injured beta cells. It is suspected that the deaths of the animals, receiving the minimum effective single doses, which occurred 18 to 30 hours after injection were caused by the lack of insulin (Ridout, Ham and Wrenshall, '44; Bailey, Bailey and Hagan, '44). This interpretation is supported by the cytological evidence of extensive injury to the insulin secreting beta cells. However, confirmation from adequate blood sugar determinations is lacking.

SUMMARY

The minimum effective dose of alloxan for the frog was found to be within the range of 150 to 220 mg. per kilogram of body weight. Doses of this order usually caused death of the animal within 18 to 30 hours and were effective in inducing degenerative changes in the beta cells of the pancreatic islands. Higher doses usually resulted in earlier death of the animals, before histological evidence of injury of the pancreas became obvious. Lower single doses usually were ineffective.

The changes in islets of Langerhans occur much more slowly in the frog than in mammals and are not readily recognized until 8 to 10 hours after the injection. Degranulation of the beta cells is followed by vacuolation of the cytoplasm and in advanced stages the cytoplasmic volume is greatly reduced, with loss of vacuolation and apparent disappearance of cell boundaries. The nuclear changes are limited. There is little pycnosis but some swelling. Complete necrosis of the islands was not observed.

The architectural pattern of the islands is also lost. The cords of beta cells are transformed into irregular compact masses. Capillary dilatation is characteristic of the early phases of injury but in later stages the capillary supply is greatly reduced or almost absent. Slight changes in the alpha cells are interpreted as secondary to the injury of the beta cells and to the reduction in blood supply to the island.

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EXPLANATION OF PLATE

All figures were outlined by means of a camera lucida at a magnification of 860 diameters. The sections were cut at 5 micra.

PLATE 1

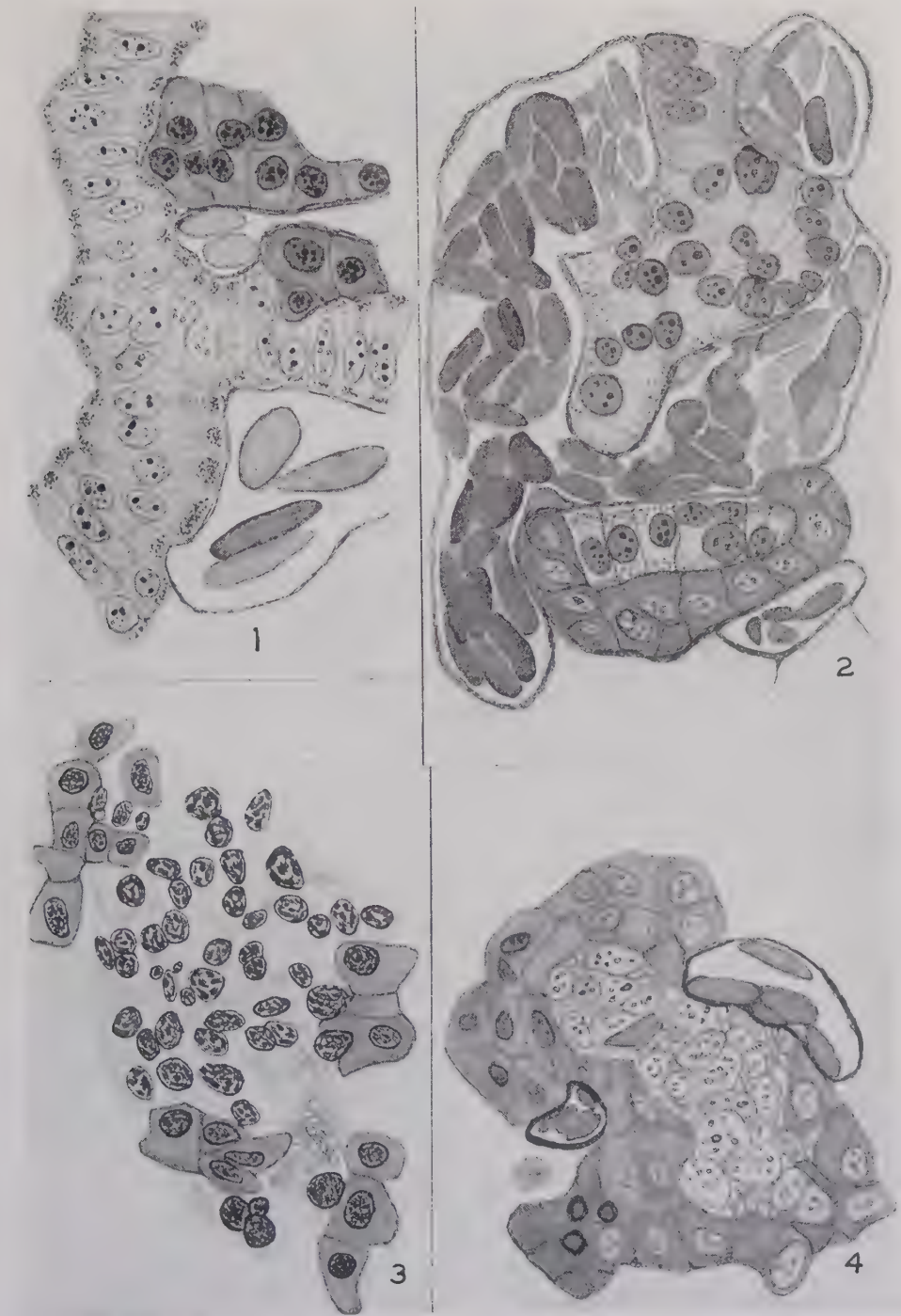
EXPLANATION OF FIGURES

1 A portion of a normal islet showing the typical pattern of beta cords and groups of alpha cells. In many beta cells the granules have a bipolar distribution. The alpha cells are densely filled with fine granules of uniform size. Bouin fixation; Gomori's chrome hematoxylin-phloxin method.

2 A portion of an islet 4 hours after the injection of 550 mg. per kilogram of body weight of alloxan. The beta cells show slight evidence of distortion with little degranulation. The capillaries are remarkably distended. Helly fixation; Heidenhain's azan method.

3 A portion of an islet 24 hours after the injection of 280 mg. per kilogram of body weight of alloxan. The beta cells are completely disorganized and all granules have disappeared. Cell outlines are indistinct or obliterated and some vacuolation is present. The grouping of the alpha cells is also disturbed, probably due to the disorganization of the cords of beta cells and the loss of the capillary supply. Helly fixation; Gomori's chrome hematoxylin-phloxin method.

4 A portion of an islet 30 hours after the injection of 150 mg. per kilogram of body weight of alloxan. The cord-like pattern of the beta cells has disappeared and the residual, apparently confluent, cytoplasm of the cells is highly vacuolated with a complete loss of specific granulation. The nuclear patterns are almost normal with some evidence of nuclear swelling. The massing of alpha cells is probably due to the contraction of the beta cords and the compacting of the cells. The pycnotic nuclei seen in some cells may be due to the reduction in the capillary supply. Helly fixation; Heidenhain's azan method.



THE INJURIOUS EFFECT OF LIGHT UPON DIVIDING CELLS IN TISSUE CULTURES CONTAINING FLUORESCENT SUBSTANCES

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ONE PLATE (EIGHT FIGURES)

Fluorescence is a property of certain substances that causes them to emit light when activated by ultra violet light. In most instances the light emitted is differently colored from that of the substance. In minerals containing a fluorescent material it was found possible to photograph in the dark, by means of ultra violet light, the site of the fluorescent material (Thornton and M. N. Lewis, '34).

Biologists are acquainted with this phenomenon because certain dyes and oils change color in the sunlight, as for instance eosin, chlorophyll and machine oil.

The lethal effect of light upon animals that have taken in hematoporphyrin has been known for many years. The photosensitivity of living cells stained with vital dyes was discovered when W. H. Lewis made motion pictures of living cells stained with neutral red.

Menke, J. F., in 1935, found that cancer cells growing in tissue cultures containing eosin were more photosensitive than normal cells in the same culture.

MATERIAL

Dividing cells in hanging drop cultures of chick embryo tissue were selected as the material for these investigations because previously it had been found that while living cells in tissue cultures are delicately balanced in relation to the medium surrounding them (Lewis, '18, '20, '21, '23; Hogue, '19; Dederer, '21; and Rich, '24), the dividing cells in growing cultures are more sensitive to changes in their environment than the resting cells since they showed the effect of acids, alkalies, dyes, ether, heat, osmotic pressure, radium and colchicine earlier than the resting cells in their immediate neighborhood (Bauer, '25; Lewis, '33, '34, '35; Rosenfeld, '32, '33; Whitman, '33; and Lahr and Riddle, '38).

METHOD

Three tiny pieces ($1 \times 1 \times 1$ mm.) one of skin, one of connective tissue, and one of muscle taken from a chick embryo that had been incubated for 7 to 9 days, were placed in a drop of sterile Locke-Lewis solution (80 cc. Locke's solution plus 20 cc. of chicken bouillon, plus 0.5 gm. of dextrose) on a sterile cover glass suspended over a hollow ground slide. The cover glass was sealed to the slide by means of sal-voline. Each series had ten cultures in Locke-Lewis solution and an equal number in the same medium containing one of the following fluorescent substances, namely, chlorophyl, 1:2:5:6-dibenzanthracene, methylcholanthrene, neutral red or eosin. Many series of cultures containing fluorescent substances as well as control cultures were studied.

Chlorophyl was obtained by the extraction of leaves of spinach or of grass in 95% alcohol, filtering off the extract and then removing the alcohol by distillation until a thick green material was obtained. The neutral red was an intra vitam dye and the eosin was a water soluble dye.¹

Chlorophyl, dibenzanthracene and methylcholanthrene were not soluble in the nutrient medium and so each of them were ground to a fine emulsion in the medium before it was added to the cultures.

The amount of each substance that could be added to the cultures without damaging the tissue growing in the dark had to be determined by making a series of cultures containing graded amounts of each substance, and then selecting the amount that permitted the most abundant growth while at the same time inducing photosensitivity.

The amounts used were chlorophyl, dibenzanthracene and methylcholanthrene 1 to 50,000 and neutral red and eosin 1 to 100,000.

In the majority of tissue cultures where the cells grow out in a thin layer the mitotic spindle becomes orientated with its long axis in the plane of the cover glass (figs. 1, 3, and 5). This orientation renders observation of the changes in the spindle and of the chromosomes under experimental conditions easier than if the plane of division is at an angle.

The cultures were examined first under the microscope of the motion picture apparatus by means of a dull filtered light in order to locate a field containing one or two dividing cells. The filter was then removed and the cells were exposed to the light ordinarily used in taking motion pictures of living cells (6 volts, 108 watts, ribbon filament with a 1-inch water filter to prevent heat). The subsequent behavior of the cells was recorded by means of motion pictures.²

¹ Prepared by Gröbler and Company.

² Motion pictures showing these changes are available.

RESULTS

The fluorescent substances, chlorophyll, dibenzanthracene, methylcholanthrene, neutral red and eosin, added to the tissue cultures were not toxic so long as the cultures were kept in the dark. In the dark the cells in media containing these substances grew and multiplied, exhibiting about the same number of mitotic figures as the control cultures growing in media free from fluorescent material. It was only when a strong light was passed through a culture containing a fluorescent substance that the cells became damaged.

Cells in the prophase stage of division growing in a medium containing neutral red or eosin when exposed to light failed to form a spindle. The scattered chromosomes became shrunken and stationary. Later these cells formed many blebs.

As the light activated the fluorescent substance the spindle of the cell in metaphase shortened and later disappeared; the mitochondria and other granules moved into the area previously occupied by the spindle and the chromosomes became agglutinated. The chromosomes failed to separate and remained clumped on the equatorial plate (figs. 2, 4, 6 and 7).

The photodynamic action affected the cytoplasm of many of the dividing cells so that blebs such as those described by Cash, Bauer and Rosenfeld appeared on the surface of the affected cells (figs. 3, 5 and 6). In such cultures the blebs arose first on the processes of the dividing cells (fig. 5) and resembled those that in many instances develop on the processes of normal dividing cells. In most instances if the light was not removed many more and more fluid blebs (fig. 6) appeared on the body of the cell similar to those described by Menke ('35), when cells were irradiated in a medium containing phloxine. Later active circus movement of the fluid blebs took place. Under longer exposure to the light the cells died and the blebs became quiescent (figs. 7 and 8).

The majority of the cells in anaphase in cultures containing neutral red or eosin when exposed to light failed to complete their division, but in a few instances the cells in late anaphase indented and were almost completely separated before the light caused a cessation of the division resulting in a failure of the sister cells to separate. Some of the cells that had been prevented from separating into the sister cells later fused and formed binucleate cells. In many of the cells affected in the early anaphase stage the chromosomes remained attached end-to-end as has been described in cultures having fluorescent x in their medium (Lewis, '35). In dying cells the chromosomes became clumped

into a small area regardless of the stage of division at which they were affected.

In some instances the medium on one-half of the control cultures growing in Locke-Lewis solution was changed to one made up of chicken plasma containing a fluorescent substance. Such cultures gave better results because chlorophyll, dibenzanthracene and methylcholanthrene could be ground to a more homogeneous suspension in plasma than in nutrient salt solution. Although the growth exhibited in these cultures was more extensive than that in cultures in nutrient salt solution irradiation of the fluorescent substance damaged the dividing cells in the same manner regardless of the medium in which they were growing.

When the cultures that had reacted to light were returned to the dark before they were greatly damaged, the resting cells continued their normal behavior so that when the cultures were examined 12 to 24 hours later, there were many cells in normal division. On the other hand cells that developed many blebs, circus movement or agglutinated chromosomes either died or were so abnormal that they failed to recover even in the dark.

After fixation, by means of Bouin's solution, of the treated cultures containing dividing cells it could be seen that the centrospheres instead of remaining at the ends of the cell had drawn close to the equatorial plate of the chromosomes. In some fixed preparations coagulated spindle fibers extended from the centrosphere to the nearby edges of the equatorial plate of the chromosomes and formed greatly shortened spindles.

The injurious results were apparently not due to the light emitted by the activated fluorescent substance as was found also by Menke ('35) for the cells continued to grow normally when light reached them after passing through a few drops of medium containing neutral red or eosin placed in the bottom of the hollow ground slide only a slight distance away from the growing tissue.

From these experiments it seemed evident that cells were damaged by the change brought about in the medium during the activation of the fluorescent material present in the medium in which the cells were growing.

The injurious effect was not one that acted coincidentally on living tissue, for resting cells in many of the cultures in which the dividing cells had died, when returned to the dark later exhibited growth and normal division.

Not all of the photodynamic substances used became activated with the same rapidity when exposed to the same intensity of light, at least they did not bring about perceptible injuries in the living cell with the same rapidity. Chlorophyl, dibenzanthracene and methyleholanthracene affected the living dividing cells more slowly than neutral red or eosin. When cultures containing the former compounds were exposed to light, the first dividing cell brought into the field of light in some instances completed its division while a neighboring cell in an earlier phase of division became affected by the light as it came into metaphase, and failed to complete its division. On the other hand dividing cells growing in media containing neutral red or eosin when exposed to the light of the same intensity rapidly became injured and failed to complete their division.

DISCUSSION

Many investigators have attempted to explain the photodynamic action of substances such as dyes, chlorophyl, cutaneous excretion of pellagra patients and the pigment of the Harderian gland of mice.

Sacharoff and Sachs ('05) and Blum ('30 and '32) showed that hemolysis was brought about when red blood cells in dilute concentrations of a photodynamically active substance were exposed to sunlight. Wood ('22) found that the adsorption spectrum of fluorescein shifts toward the red end of the spectrum when photofluorescein is produced following the exposure of the dye to light.

Menke ('34) showed that when fluorescein was exposed to irradiation by sunlight for 300 hours a compound named photofluorescein was obtained that was capable of producing hemolysis of red blood cells in the dark to the same extent that fluorescein did in the sunlight.

Lewis ('35) found that cells growing in a culture containing a fluorescent substance exhibited greater photosensitivity than those in cultures to which the fluorescent material had just been added.

Lewis ('35) also found that fluorescent x which is a form of reduced neutral red (Clark, '32) brought about abnormalities in the mitosis of cells in tissue cultures even in the dark. The dye, however, soon became changed to neutral red by the action of the living cells, after that the normal behavior of the dividing cells was disturbed only when the cultures were exposed to a strong light.

Menke ('35) irradiated cultures by means of a Leitz-Wetzlar 4-5 ampere alternating current carbon arc lamp at a distance of 18 inches with a water filter placed in the incident ray to absorb the heat. Menke used a much stronger solution of the dye (1 to 1000 or

1 to 1500) than we used in our experiments (1 to 50,000). He found that the malignant cells were affected after 5 minutes irradiation while the stroma cells of the same cultures remained in normal health.

Ultra violet light penetrated living tissue too short a distance to activate dyes injected into the animal. Therefore, many investigators have hoped to find a photo compound of some fluorescent material that can bring about in vivo the injurious effect that exposure to light does to cells in cultures containing fluorescent substances. So far, however, the few photocompounds obtained have been rendered inactive by the conditions existing in the living animal.

It was found by Lahr and Riddle ('38) and by Paff ('39) that colchicine arrested the mitotic division of cells in the metaphase stage in vivo. This was looked upon as a means of destroying growing cells until Bernard ('39) found that many of the resting cells survived and continued their normal division after the effect of the drug had subsided.

CONCLUSION

Cells of chick embryos growing in tissue cultures in media containing fluorescent substances divided and grew normally in the dark, but when exposed to a bright light the dividing cells became abnormal, while the resting cells exposed to the same intensity of light were not injured. During the exposure to light the spindle of the dividing cells shortened, the mitochondria and other granules moved into the area previously occupied by the spindle, the chromosomes became agglutinated on the equatorial plate, many blebs developed on the surface of the cells and division failed to be consummated.

When cultures in which the dividing cells had been injured by light, activated fluorescent substances were returned to the dark incubator for a few hours, the resting cells exhibited many normal mitotic figures. A few of the dividing cells that had been injured only slightly recovered and completed their division, but the majority of them died.

This type of differential injury was not peculiar to the cells growing in light activated media since it had been demonstrated previously that dividing cells were injured more readily than resting cells in cultures treated with acids, alkalies, ether, heat, fluorescence x, radium and colchicine.

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PLATE 1

EXPLANATION OF FIGURES

1 Normal fibroblast in the metaphase stage of division growing in a medium containing chlorophyl.

2 The same cell after exposure to light for 42 minutes. The spindle area has been invaded by mitochondria and other granles although the fat globules have retained their position on the surface of the cell. The chromosomes are agglutinated, but there are few blebs.

3 A cell in metaphase growing in a medium containing methyleholanthrene. The spindle with the mitochondria and the fat globules on the surface of the cell can be seen. A few blebs have formed on the processes of the cell.

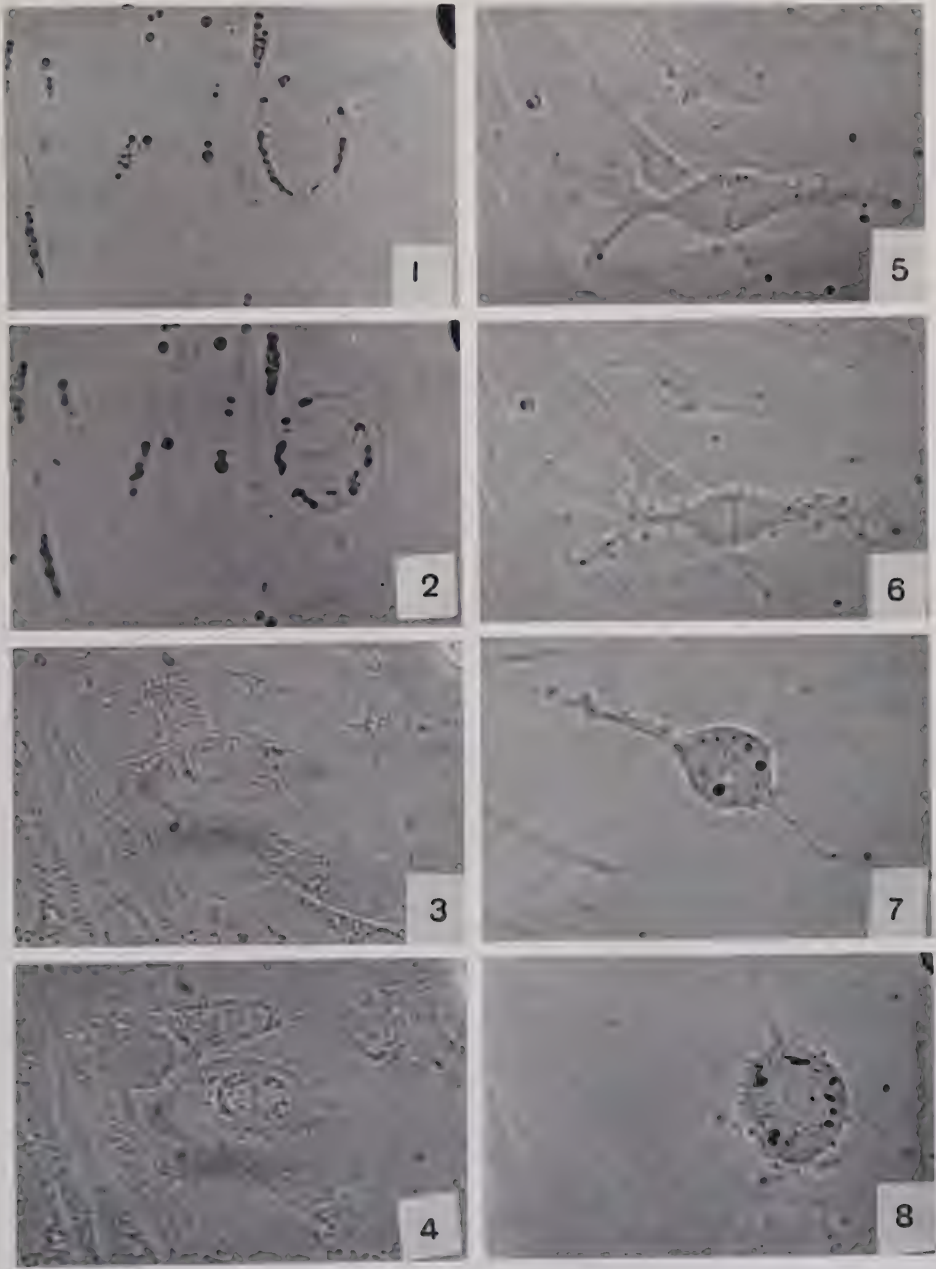
4 The same cell after 14 minutes exposure to light. The spindle has disappeared and even the fat globules have moved into the area previously occupied by the spindle. Some blebs are present on the body of the cell and the chromosomes have become agglutinated.

5 A dividing cell growing in a medium containing neutral red. The spindle is clear; the chromosomes are arranged on the equatorial plate, and a few blebs are present on the processes of the cell.

6 The same cell after 11 minutes exposure to light. Many blebs are present on the processes and also on the body of the cell. The chromosomes are agglutinated on the equatorial plate. Granules occupy the region of the spindle.

7 A dividing cell growing in a medium containing neutral red beginning to be damaged by the light as can be seen by the loss of its spindle, the agglutination of the chromosomes, and the formation of blebs.

8 A dividing cell in a medium containing neutral red that died after exposure to light. The spindle has disappeared, the chromosomes are distorted and the blebs have ceased their circus movement.



THYROIDECTOMY IN THE NEWBORN RAT¹

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FOUR FIGURES

Salmon observed that the removal of the thyroid gland in the rat shortly after birth greatly retarded development and also shortened the life span to 40–60 days. (Salmon, '36, '38, '41; Ziskin, Salmon and Applebaum, '40). The thyroidectomies were performed on rats of the Long-Evans strain at 1–2 days of age. They were anesthetized by refrigeration at 5–10°C. for 30 minutes. The anesthesia did not affect the growth of normal rats. The rats were fed a diet of "lettuce and special rations for adult lactating rats". The upper tracheal region of each experimental animal was serially sectioned and examined for thyroid remnants. Thyroidectomy at older ages (7 and 14 days) produced less marked retardation in development. The rats thyroidectomized at birth displayed a peculiar leveling off of growth at the age of 3 weeks. At this age, they reached their maximum body weight (25–35 gm.) and skeletal size. There was no further development of the skeletal structures after this age. The skeletal development at 22 days corresponded to that of the normal rat of 14 days of age. These rats showed retardation also in the opening of the eyes, in the development of the gonads, teeth, hair, adrenals and thymus. They were susceptible to infection and "acute intestinal stasis," both of which Salmon felt shortened the longevity of the thyroidless rats. These rats were subject to violent attacks of tetany which occurred either spontaneously or were induced by ether anesthesia.

As Salmon found that the retardation of growth in these rats thyroidectomized at birth was not repaired by injections of pituitary growth extract or by pituitary implantations, it was of interest to repeat the experiment and see if the animals would respond to injections of purified growth hormone. In order to do this, the experimental animals had to be prepared and their characteristics studied (Scow, '43). This paper is devoted to the characteristics of the thyroidless rats. The

¹ Aided by Grants from the Research Board of the University of California and the Rockefeller Foundation, New York City.

following paper (Scow and Marx, '45) describes their response to growth hormone.

EXPERIMENTAL PROCEDURE

Thyro-parathyroidectomy was performed on a total of 440 rats (Long-Evans strain, the same strain employed by Salmon), on the first or second day of life. Litters of eight were chosen, of which six were thyroidectomized and two (one male and one female) were retained as controls.

Refrigeration anesthesia was used. The rats were placed for 15 minutes in a beaker in which the temperature was -5 to -10°C . The resulting anesthesia lasted 8 to 15 minutes. Certain skeletal anomalies developed in the limbs of the anesthetized rats which came in contact for too long a period with the surface of the cold beaker. Normal animals similarly anesthetized showed these anomalies with the same frequency, yet did not display any appreciable reduction in body weight increase (Scow, '44 b).

During the first 4 postoperative days, half of the operated rats usually died, reducing the number of thyroidectomized rats in the litter to two or three. Rats were weaned at 28 days of age. The temperature of the room in which they were kept was 25 – 29°C . After weaning, six to eight animals were maintained in a cage (normals, 3–4 per cage). The diet was McCollum's Diet I,² which was always available in the cage in the dry form. In addition, small amounts were mixed with water and fed in the evening. The animals showed a marked preference for this wet mash. The diet was not supplemented by lettuce. After the first 4 postoperative days, only a few animals died. At the termination of the experiment, all animals were in excellent condition. A total of twenty-six completely thyroidectomized rats (18 injected, 8 uninjected) were sacrificed when 56 to 141 days of age. (Preliminary report of results, Scow, '43, '44 a.)

RESULTS

The following were the chief effects of complete thyroidectomy of the newborn rat upon subsequent development:

1. During the first 30 days, the rats were weak and displayed marked impairment of locomotion. Within the next 12–20 days, the locomotor difficulty and the weakness tended to disappear, and they were able to climb up the side of the cage. After 45 days of age, they played with each other as did normal animals. During the day, the dwarfs were

² McCollum's Diet I slightly modified, consisted of whole wheat 67.5%, casein 15%, whole milk powder 10%, NaCl 1%, CaCl_2 1.5%, homogeneous vegetable oil 5% and a concentrate of fish oil in amount to give 1.52 Chick Units of vitamin D and 11.4 USP units of vitamin A per gram.

frequently seen huddled together sleeping. They were slow to awaken, but when aroused they would display an unexpected amount of activity.

2. There was some tendency for excessive accumulation of gas in the intestines as shown by the roentgenograms (14 out of 83 cases). Only three of these animals died. The accumulation of gas was correlated with the occurrence of a protuberant abdomen.

3. Thyroidectomized animals did not show increased susceptibility to infection. Spontaneous tetany was not observed in any of the animals. Each thyroidectomized rat was roentgenographed at least three



Fig. 1 Littermate male rats 89 days of age. The white rat was thyroidectomized during the first day of life and now weighs 49 gm., whereas its normal control weighs 342 gm. The skeletal age of the thyroidectomized rat, as shown by roentgenogram, is 18 days (fig. 5 of the following paper, Scow and Marx, '45). The infant-type hair of the dwarf may be contrasted with the adult-type hair of the control.

times and each time it was anesthetized with ether for a period of 5 to 40 seconds. Tetany was not observed at these times.

4. Marked retardation of body weight increment was observed. The resultant dwarfism is strikingly illustrated by the contrast between an 89-day-old thyroidectomized male rat and its normal littermate control, seen in figure 1. A constant daily increase of 0.3 gm. in the body weight, however, was observed even as late as 76 days (fig. 2). No difference was observed between males and females.

5. The same retardation was observed in skeletal growth, as measured from the roentgenographic image of the tibia. As in the body weight, skeletal increase was also observed to continue slowly for a long period (as late as 56-69 days, fig. 3).

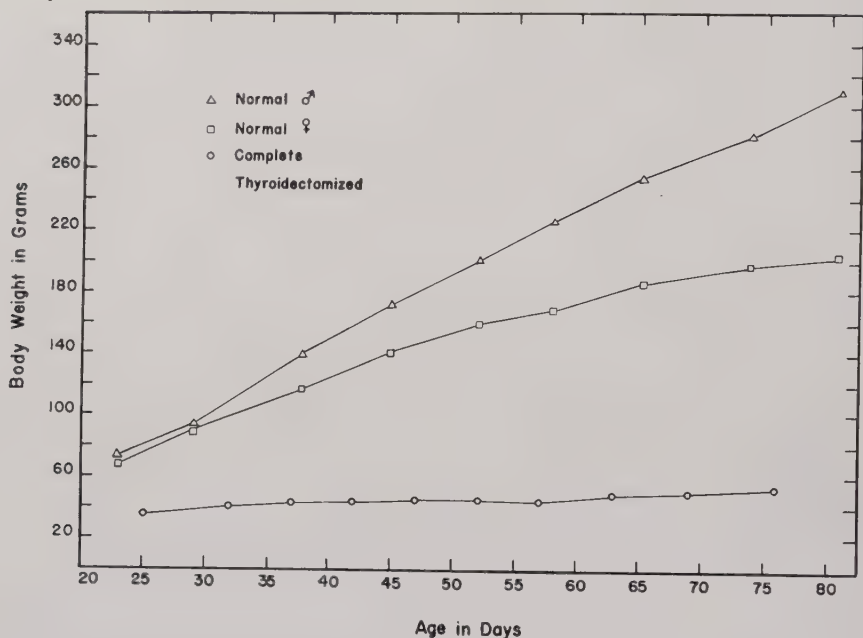


Fig. 2 Body weights of thyroidectomized and normal control rats. (Six or more thyroidectomized, 9 normal-males, and 17 normal females were used.)

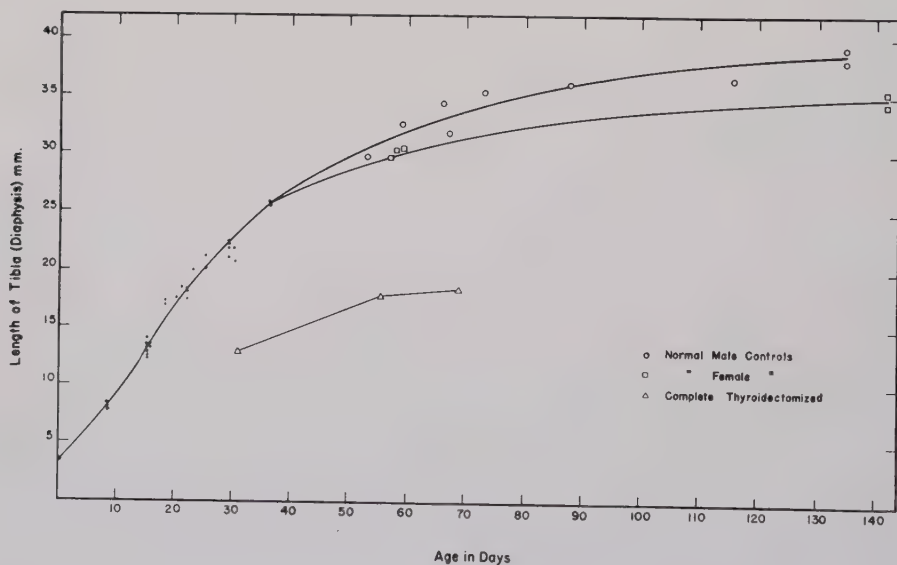


Fig. 3 Length of the diaphysis of the tibia in thyroidectomized and normal control rats. Seven thyroidectomized rats were used. Each point, square, or circle represents one animal in the normal control curve. The normal males and the normal females were not separated in this graph before the fiftieth day because no difference was observed in the length of the tibial diaphysis, both indicated by points.

6. At the chronological age of 31 days, the thyroidectomized rat had a bony development comparable to that of a 15-day-old normal rat (25 thyroidectomized rats) as determined by study of roentgenograms; at 56 days, the skeletal age had advanced only 3 days (10 animals). These ages of the bones were determined by comparison with the age of the appearance of various ossification centers in the normal rat.³ The determinations made in normal rats corresponded closely with those of Spark and Dawson ('28). The ends of the diaphyses of various long bones were enlarged, being wider than the corresponding parts in normal control rats of the same skeletal age.

7. The oxygen consumption of twenty-nine completely thyroidectomized rats was about 24% less than that of normal animals.⁴ From figure 4, it is evident that age plays a relatively unimportant role in the metabolic rates of the thyroidless rats. One of the most striking points is that no difference was detected between the oxygen consumption of the completely thyroidectomized animals and of those in which small fragments of thyroid tissue could be detected by radio-autography. Among the incompletely thyroidectomized rats tested were several animals which grew at a rate nearly half that of normal animals, yet had a metabolic rate not markedly different from that of the completely thyroidectomized animals. It is clear that the measurement of the metabolic rate confers an inadequate indication of the amount of thyroid tissue when the latter is present in small amounts. The oxygen consumption was determined on an apparatus employing the open circuit gravimetric method as devised by Haldane. It is realized that there is disagreement between various workers concerning the computation of the surface area of normal animals (Kibler and Brody, '42). The question may also be raised that the thyroidectomized animals may be so oddly shaped that the ordinary formula for computing the surface area of normal animals cannot be applied. To test the latter would involve more extensive study than could profitably be carried out in this

³ Skeletal development of normal rats at 15, 18 and 21 days as determined with roentgenogram: At 15 days: All of the epiphyses were present in the extremities except those of the head of the femur and of the phalanges of the hind feet. There were only five tarsal and four to six carpal bones. None of the caudal vertebrae had epiphyseal centers calcified. The average length of the tibia was 12.9 mm. At 18 days: the epiphysis at the head of the femur and in the phalanges of the hind feet had appeared. There was one more tarsal bone (total six) and one more carpal bone (total seven). The eight proximal caudal vertebrae had epiphyseal centers. The length of the tibia was 17.1 mm. At 21 days: another tarsal bone was present. The epiphyses of six additional caudal vertebrae had appeared (total fourteen). The length of the tibia was 18.4 mm.

⁴ We wish to thank Mr. Virgil Herring to whom we are indebted for the oxygen determinations.

experiment. The surface area was computed with a formula devised by Meeh (1879):

$$S = 0.09 \sqrt[3]{W^2}$$

S: Surface area in square meters

W: Body weight in kilograms

All observations at each age level were made on the same days. The animals tested were previously fasted 10–14 hours. The determinations were 2 hours long in the normal and 4 hours in the thyroidectomized rats.

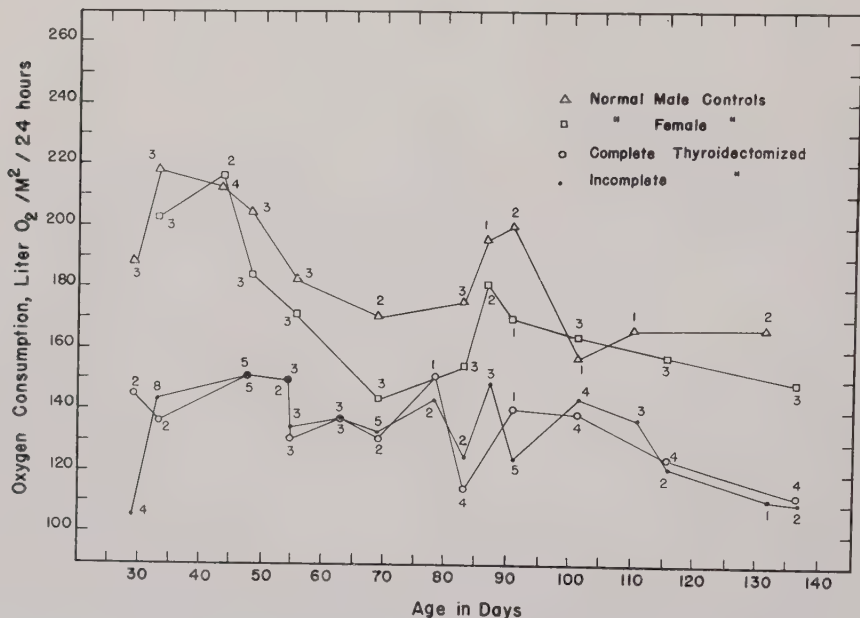


Fig. 4 Oxygen consumption of thyroidectomized, partially thyroidectomized, and normal control rats. The number at each point indicates the number of observations used to determine the value of that point.

8. The opening of the eyes and the eruption of the teeth were delayed by only a few days, which corresponds with Salmon's findings.

9. The unfolding of the pinna of the ear, from a flap of tissue overlying the future auditory meatus to the adult-shaped ear with its characteristic ridges and grooves, was delayed greatly by the removal of the thyroid gland at birth. This process took about 14 days in the normal rat, whereas it was extended over a period as long as 24 days in the operated animals. The plug which closes off the external meatus in the early post natal days disappeared at about the same age (14 days in the normal rat and 24 days in the operated rats). Evidently rats are not able to hear before the rupture of the plug, since they would not

respond to startling noises before this time. The fully developed ears of the thyroidless rats were smaller than those of the normal controls. During the early stages, an excellent indicator of the completeness of the operation was the degree of development of the ears. Histological study of the pinna showed that the development of the cartilage cells and the laying down of elastic fibers were delayed.⁵

10. The opening of the vagina was retarded as late as 100 days. (Normal 43.5 days.)

11. The transformation of the hair from the infant type (short, soft, fine) to the adult type (long, stiff, coarse) was greatly retarded (fig. 1). In the normal rat, the process was completed at about 33 days of age. The change was rapid, but accurate determination of the time required for the change was difficult because the adult type hairs were concealed by the juvenile coat until they exceeded the juvenile hairs in length. The duration of the process could be more accurately determined in thyroidectomized animals because most of the infant-type hairs fell out before the first appearance of adult-type hair and the areas of change were readily evident. In the thyroidectomized rats, the completion of the process was observed to be delayed as late as day 141 of life, the average completion being at 110 days.

12. Various organs were weighed when the animals were autopsied. The data are given in table 1. Since the numbers of thyroidectomized rats in each age group were small, every two consecutive age groups were combined so as to reduce the number of age groups to five. Since no difference in the organ weights of the male and of the female thyroidectomized rats was observed, the weights in the two sexes were combined except for the gonads. In table 2, the ratios of the organ weight to the body weight of the organs are given. The thyroidectomized rats have proportionally larger eyeballs and brains (2 to $3 \times$) than normal. The intestines of the dwarfs were proportionally ($1\frac{1}{2} \times$) heavier than those of the normals. The kidneys too were slightly larger in proportion to body weight than normal. Liver and spleen retained their normal relation to body weight. The pituitary glands were proportionally ($1\frac{1}{2} \times$) larger in the thyroidless rat. The size of the adrenal was larger than expected, the proportion to body weight being larger than in normal males, but about equal to that in normal females. The gonads (testes or ovaries) were smaller absolutely and proportionally in the thyroidectomized rats than in normal.

⁵ We wish to thank Mr. John Ainslie to whom we are indebted for preparation and analysis of the sections of ear cartilage.

TABLE 1

Organ weights of rats thyroidectomized on the first day of life compared with those of their normal littermate controls.
a. Normal male. b. Normal female. c. Injected thyroidectomized.¹ d. Uninjected thyroidectomized.

AGE AT AUTOPSY DAYS	TYPE OF RATS	NO. OF RATS	BODY WEIGHT	PITUITARY	LIVER	SPLEEN	KIDNEYS	INTESTINE AND STOMACH	BRAIN	EYEBALL	OVARIES	TESTES	ADRENALS
56-63	a	6	223	5.8	10.0	1.26	1.92	8.8	1.68	113	..	2.76	31
	b	6	171	6.3	8.2	0.70	1.62	7.1	1.57	111	49	...	44
	c	5	76	3.6	3.9	0.56	0.68	4.7	1.33	101	9(4) ²	0.28(1)	26
	d	1	57	3.2	2.6	0.29	0.58	3.7	1.40	98	9	...	21
72-76	a	6	294	6.6	11.7	0.68	2.25	10.0	1.67	118	..	2.94	38
	b	6	204	7.2	8.7	0.84	1.47	7.5	1.63	121	56	...	50
	c	3	73	3.7	3.4	0.31	0.63	4.0	1.41	111	..	0.44	21
	d	3	51	4.1	2.4	0.37	0.47	3.8	1.20	88	..	0.20	16
84-93	a	5	287	6.1	12.6	1.36	2.21	9.4	1.77	127	..	3.54	35
	b	6	196	8.0	7.5	0.81	1.50	7.4	1.68	117	61	...	61
	c	4	76	4.3	3.3	0.42	0.62	5.4	1.24	113	..	0.48	25
	d	3	67	4.1	3.0	0.38	0.60	2.9	1.25	110	13(1)	0.18(2)	22
105-111	a	1	432	6.8	13.7	1.10	2.60	11.4	1.77	157	..	3.76	20
	b	4	226	9.2	8.8	0.96	1.58	7.9	1.71	132	58	...	66
	c	3	75	4.4	3.4	0.34	0.58	4.3	1.24	110	10(2)	0.44(1)	24
	d	1	81	4.4	3.9	0.27	0.61	4.2	1.34	123	8	...	20
135-141	a	1	444	9.4	14.6	1.15	2.69	13.1	1.88	146	..	2.92	48
	b	2	250	9.4	8.0	0.84	1.61	8.6	1.78	152	47	...	53
	c	3	109	4.8	4.4	0.30	0.72	5.3	1.35	132	..	0.83	19

¹ Injected with growth hormone 2 to 41 days previous to autopsy. For details see the following paper. Organ weights of these animals are included in tables 1 and 2 as they showed no significant difference from the control in absolute or relative weights.

² Number of rats in parentheses.

TABLE 2
Ratio of organ weights to body weight.
a. Normal male. b. Normal female. c. Injected thyroidectomized.¹ d. Uninjected thyroidectomized.

AGE AT AUTOPSY DAYS	TYPE OF RAT	NO. OF RATS	BODY WEIGHT	PITUITARY 10 ⁻⁶	LIVER 10 ⁻³	SPLEEN 10 ⁻⁴	KIDNEYS 10 ⁻⁴	INTESTINE AND STOMACH 10 ⁻³	BRAIN 10 ⁻³	EYEBALL 10 ⁻⁵	OVARIES 10 ⁻⁵	TESTES 10 ⁻⁴	ADRENALS 10 ⁻⁶
56-63	a	6	223	26	46	55	87	40	73	50	..	118	14
	b	6	171	37	48	41	94	42	88	65	29	...	26
	c	5	76	47	51	74	90	62	170	130	12(4)	36	34
	d	1	57	56	46	51	100	65	250	170	16	...	37
72-76	a	6	294	24	40	23	76	34	57	40	..	100	13
	b	6	204	35	43	41	72	37	80	59	27	...	24
	c	3	73	51	47	42	86	55	195	154	..	60	29
	d	3	51	80	47	73	92	75	240	173	..	40	31
84-93	a	5	287	21	44	47	77	33	62	44	..	124	12
	b	6	196	41	38	41	77	38	80	60	31	...	31
	c	4	76	57	44	55	81	71	165	149	..	64	33
	d	3	67	61	45	57	93	43	187	164	19(1)	26(2)	33
105-111	a	1	432	16	32	25	60	26	41	36	..	86	50
	b	4	226	40	39	42	70	35	76	59	26	...	29
	c	3	75	59	45	45	82	58	167	148	11(2)	54(1)	32
	d	1	81	54	48	33	75	52	166	152	10	...	24
135-141	a	1	444	21	33	26	61	29	42	33	..	66	11
	b	2	250	38	32	34	64	35	71	61	19	...	21
	c	3	109	44	40	27	66	48	124	121	..	72	18

¹ See footnote table 1.

On microscopic examination the ovaries were found to contain only a few small follicles which were overtaken by atresia by the time they developed to the point of beginning antrum formation. The interstitial cells were atrophic. No large follicles or corpora lutea were present. The uterus was undeveloped, as was the vagina. All the reproductive system resembled closely the situation after hypophysectomy.

The testes too were undeveloped, the maximum stage of differentiation usually attained being spermatocytes.⁶ As these began to enlarge they desquamated. The Leydig tissue too was atrophic. The accessory reproductive system, dependent on the testis, was atrophic.

The adrenals, though not as atrophic as the gonads, were small. They were characterized by a thin cortex, composed of small cells containing fine lipid droplets. A narrow subglomerular zone of low lipid content was present (about the same or slightly wider than in the normal male, but narrower by far than after hypophysectomy). The zona fasciculata and reticularis were not clearly differentiated, except in a few cases where the reticularis had a lower lipid content. No differences between the adrenals of thyroidectomized males and females could be distinguished.

THE DETERMINATION OF THE COMPLETENESS OF THYROIDECTOMY

The completeness of the operation was determined by various methods, some available while the animals were alive, and some applicable only after the animals were sacrificed.

The first method, which gave presumptive indications only, was not reliable enough to detect the presence of very small amounts of thyroid tissue, but did permit selection of more from less completely thyroidectomized animals. The presumptive method took into account body weight gain, oxygen consumption, vaginal opening, gonadal development, development of the ear and the transformation of the hair from the infantile to the adult type.

The final decision for completeness of operation depended upon the analysis of the skeletal development, of the radio-autograph, and of serial sections of the tracheal region. (In the case of 16 rats, serial sections of the whole mediastinum and neck tissues were made.) Fol-

⁶ See table 3 and discussion thereof. Spermatid formation was observed in two completely thyroidectomized rats which had attained the ages of 135 and 141 days (B9, W4). Spermatozoa were observed in one male in this older age group (BH6) which was supposedly completely thyroidectomized both on the basis of radio-autograph and serial sections. The bone age of this rat however, suggested incompleteness. The situation in the case of the female BH5, was completely comparable to that in the male just mentioned. Here corpora lutea were present in an animal in which all criteria except bone age pointed toward completeness of the operation.

lowing is a correlation of the findings from the three so-called definitive methods of determining completeness of operation.

The skeletal age of completely thyroidectomized rats is 15 days at the chronological age of 31 days, and does not advance beyond 18 days by the chronological age of 56 days. Small bits of thyroid, which may lie dormant during the first 30 days, may later be stimulated sufficiently to cause a mild increase in bone development. The roentgenograms taken at 56 days of age detected this.

The radio-autography depends upon the ability of the thyroid gland to concentrate iodine many times more than any other tissue in the body (Morton, Chaikoff, Reinhardt and Anderson, '43; Reinhardt, '42). Radioactive iodine was injected intraperitoneally 36 hours before autopsy. This permitted excess iodine to be excreted. At autopsy, the tissue mass consisting of the base of the tongue, hyoid bone, pharynx, larynx, trachea, oesophagus, pretracheal muscles, thymus, heart, root of the lungs and great vessels, and all tissues adherent to this mass were dissected out in one piece and placed in neutral 10% formalin. The tissue mass was left in formalin for at least $4\frac{1}{2}$ hours before radio-autography. All tissue masses were exposed for at least two different lengths of time — 18 to 24 hours, and for 70 hours. A satisfactory radio-autograph was obtained with the use of Eastman Ultra-Speed Safety X-ray Film. Of forty animals thought to be completely thyroidectomized, the tissue masses of only twenty-six gave no evidence of the presence of iodine-concentrating tissue as determined by the radio-autograph. Tissues of the remaining fourteen rats produced faint images.

Serial sections, cut at 15 to 20 μ , were examined microscopically for thyroid fragments in twenty-two of the fifty-three rats autopsied. The whole tissue mass, from tongue to heart tip, was examined in ten of the twenty-three animals in which the radio-autographs were negative. In those instances in which tissues were cut from animals where the radio-autographs indicated fragments were present, only that area giving the positive image was examined serially. The results of the histological analysis are given in table 3 and are there compared with other methods for gauging completeness. It will be noted that bone age at 30 days chronological age is included, as this was used as the most important single criterion for judging completeness in selecting living animals for experimental work. By comparison of this criterion with others given in the table it will be seen that all incomplete cases were not eliminated by this means. By the fifty-sixth day of age, bone age is a more reliable criterion of complete thyroidectomy. It will be seen

TABLE 3
Correlations of different methods of judging completeness of operation in rats thyroidectomized at birth.

RAT NUMBER	BODY GROWTH AT					THYROID REMNANTS PRESENT JUDGED BY		OXYGEN CONSUMPTION		Ovaries		GONADS	
	30 days of age		Autopsy			Radio- auto- graph	Serial sections ¹	Age	1.02/m ² /24 hr.	Weight	Structure ⁴	Weight	Testes
	Body wt. gm.	Bone age	Age	Body wt. gm.	Bone age								
BH53 ² ♀ BH60 ² ♂	15 <15	das. 15	56 56		das. 18 <18	— —		54 das.	150	6 mg.	sF, IT atrophic	276 mg.	Maximum differentiation stage in tubules
GH39 ² ♀ B66 G28 BH57	<15 40 45	<15 >15 18	56 56 56 56	57 52 69	18 18 21 <29	— — + +	— — + +	52 54 54 54	150 166 156	4 9 4 7	Same Same Same Same		Few spermatoocytes; IT like CT cells
BH48 ² ♀ BH50 ² ♀ GH33 ² ♀		15 <15 15	63 63 63		18 <18 29	— — +		38 33	127 147 97	9 9 14	Few smF; IT atrophic Same Several lF		
GH31 ² ♂ GH32 G21 ² ♂ BH45 ² ♂ GH29 ♂ W42 ♂		<15 15 15 <18 36 38	72 72 72 72 72 72		18 18 18 <29 60 80	— — — + + +		69 69 69 69 69	136 173 128 110 137 116	316 270 696 1214 224 596	Spermatoocytes, desquamating; IT like CT cells Same Spermatoocytes, many; IT like CT cells Spermatoocytes, many; IT like CT cells Spermatoocytes, 1-2 layers; IT like CT cells Same		
B49 ² ♂ W36 ♂ G15 ² ♂ B50 ² ♂ W37 ♀		15 <15 <15 15 <15	76 76 76 76 79		18 18 18 18 52	— — — — —	— — + ³ + ³			7 152	3-4 mF; IT	234 192 756 946	Same Spermatogonia, few; IT epithe- lioid Spermatoocytes, many; IT epi- thelioid Same

that results of examination of serial sections of the neck agree closely with decisions reached from the radio-autograph, the only exception being in two cases (G15 and B50) in which the radio-autographs were negative and yet thyroid fragments were found in section. As noted in the table, however, the thyroid tissue did not appear normal in these cases and might not have been functional. (The colloid appeared to be very hard, it chipped easily, did not take a clear red eosin-stain as is usual, but was darker staining due to the absorption of some hematoxylin. The epithelium of the fragments was exceedingly flat and in some places was not distinguishable from other cells concentrically arranged around the colloid.) It will be noted further in the table that in

TABLE 4

Correlation of the most reliable methods for determination of completeness of operation in rats thyroidectomized at birth.

NO. OF RATS	RADIO-AUTOGRAPH	SERIAL SECTION	SKELETAL AGE IN DAYS AT THE FOLLOWING CHRONOLOGICAL AGES			
			30 days	56-76 days	84-105 days	135-141 days
10	Negative	Negative	15	18 (2) ¹	21 (1) 18 (2)	29 (3) 36 (2)
2	Negative	Positive ²	15	18	..	..
10	Positive	Positive	15-18	21 (1) ³ 29 (7)		36 (2)

¹ Numbers of rats on which determinations were made are placed in parentheses in those cases where the whole group was not examined.

² From microscopic evidence probably tissue was non-functional

³ Chronological age 56 days; in other seven cases determinations were made in the latter part of the period.

at least two other instances (BH 5 and BH 6), both radio-autograph and serial sections were negative, yet bone age was too far advanced (36 days and above, at a chronological age of 141 days), thus indicating incompleteness. It should be noted that in the last mentioned animals the gonads too showed unusual development. The oxygen consumption is also included in table 3, but as will be seen it was not helpful in determining completeness of operation. It is true the metabolic rate was low in all cases, even where small thyroid fragments were found to be present, but the variation was considerable.

Table 4 compares briefly the three best methods for determination of completeness of thyroid removal in rats thyroidectomized on the

first day of life. In brief, either radio-autographs or serial sections made of the thyroid region furnished sufficiently reliable evidence for judging completeness. Bone age was no less reliable and in addition was available during the life of the animal. It should be added however, that bone age at 30 days of age had not quite as high a degree of reliability as at 56 days chronological age.

TABLE 5

A comparison of the findings of Salmon with the findings reported here concerning the effects of thyroidectomy of the rat at birth.

	SALMON'S FINDINGS	FINDINGS REPORTED HERE
<i>Age at time of thyroidectomy</i>	1-2 days	1-2 days
<i>Weaning age</i>	23 days ¹	28 days
<i>Body weight²</i>		
Age (days)	grams	grams
22	23	..
25	..	34
40	25	44
60	27	49
75	..	53
<i>Skeletal age</i>		
Chronological age in days	Bone age in days	Bone age in days
22	13	..
32	..	15
40	15	..
60	15	18
<i>Occurrence of tetany</i>		
Spontaneous:	Occasionally	None
Induced by ether anesthesia:	Frequently	None
<i>Susceptibility to infection</i>	Main cause of death	Not increased
<i>Intestinal stasis</i>	Main cause of death	Infrequent
<i>Age when vagina opened</i>		After 100 days ³
<i>Completion of transformation of hair</i>		110 days (average) ³
<i>Longevity</i>	60 days	141 days ⁴

¹ Salmon concluded that there was "no evidence for any factor in mother's milk which might be responsible either for early growth or for cessation of growth". In this experiment, the rats were left with the mother until day 28 because they remained in better physical condition than when weaned earlier.

² In Salmon's studies, the body weight of thyroidectomized rats at 22 days of age was 48% that of the normal male controls, whereas in these studies, they weighted 42% of normal.

³ In experiments reported by Salmon, animals died at an age which would not permit observation of these phenomena.

⁴ The experiment was terminated when the maximum age attained was 141 days; all of the animals appeared to be in excellent condition.

DISCUSSION

When the results of this experiment are compared with the findings of Salmon, several outstanding things are observed (table 5). The completely thyroidectomized animals reported in this experiment had a greater longevity, no increased susceptibility to infection, and no complete cessation of the differentiation and growth of the body and the skeleton. On the assumption that the methods used here for determining completeness of operation are adequate, it is concluded that the rat is able to grow slowly and differentiate during the period studied in the complete absence of the thyroid gland from time of birth. The essential difference from normal is the greatly reduced rate. Considering the numerous sensitive tests used here to determine completeness of the removal of the thyroid gland, including those used by Salmon, it is felt that the results obtained by Salmon — plateau in growth and differentiation after 3 weeks of age, short life span (40–60 days), and susceptibility to infection — cannot be referred to the lack of thyroid alone, but must be attributed to some additional factors.

SUMMARY

The principal effect of thyroidectomy at birth in the rat was manifested as a marked retardation in the growth and maturation of the animal. The rat thyroidectomized at birth had the following characteristics:

Exceedingly slow but continuous increase in body weight and size of skeleton.

Delay in appearance of secondary ossification centers.

Reduction in oxygen consumption.

Marked retardation in the transformation of hair from the infant to the adult type.

Delay in opening of eyes and eruption of teeth.

Retarded development of the ear and delay in rupture of the plug in the external auditory meatus.

Delay in the opening of the vagina.

No apparent increase in susceptibility to intestinal disorders and infection.

Hearty appetite.

Unexpected degree of motor activity when aroused.

No symptoms of tetany.

The eyeball and the brain of the thyroidectomized rats were practically equal in absolute weight to those of the normal rat, therefore being greater in proportion to body weight. The intestines likewise were proportionally larger in the thyroidless rats.

Kidneys, too, were slightly larger proportionally. The liver and spleen had the same proportion to body weight as was characteristic of the normal.

The proportion of the adrenal weight to the body weight was greater in the normal female rats than in the normal males; in the thyroidectomized rats of both sexes the proportion was high, being comparable to that in the normal females.

The gonads and dependent accessory organs were markedly sub-normal in development.

The morphological and physiological characteristics of the living animals were valuable aides in judging completeness of thyroidectomy for purposes of choosing rats for experimental purposes. The definitive proof of completeness, however, rested on three equally valuable criteria — serial section of the thyroid region, radio-autograph, and skeletal age.

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RESPONSE TO PITUITARY GROWTH HORMONE OF RATS THYROIDECTOMIZED ON THE DAY OF BIRTH¹

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FOUR TEXT FIGURES AND TWO PLATES (FOUR FIGURES)

It is well established that normal growth is dependent upon the secretions of both the thyroid and the pituitary glands. It has been demonstrated that the pituitary contains a factor which can stimulate growth in rats in the complete absence of the pituitary or thyroid, or of both glands (Smith, '27, '30, '33; Evans, Simpson and Pencharz, '39). In all these types of rats the growth response is better if thyroid extract is given concurrently with the growth hormone (Smith, '33; Evans, Simpson and Pencharz, '39). In these studies and in the earlier work of Flower and Evans ('25), in which a response to growth hormone was reported in thyroidectomized rats, the animals were thyroidectomized after weaning. Salmon ('38, '41) in repeating this work, removed the thyroid at birth and was unable to correct the resultant dwarfism by the administration of either anterior pituitary growth extracts or pituitary implants. In view of these contradictory results, Salmon suggested that the important factor involved appeared to be the age of the animal at the time of the thyroid ablation, that in very early post-natal life animals can not respond to hypophyseal substances without the thyroid.

The purpose of this study was to repeat Salmon's interesting experiments, to see whether, employing a purified growth hormone preparation of adequate unitage, we could confirm the report of the lack of growth response of rats thyroidectomized at birth.

EXPERIMENTAL PROCEDURE

Growth hormone preparation. The anterior pituitary growth hormone used was a cysteine treated globulin fraction (Marx, Simpson and Evans, '42, '43) which was practically free of other known pituitary

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hormones.² The growth hormone was injected daily, intraperitoneally, in 1 mg. doses, dissolved in 0.5 cc. of physiological saline solution. This daily dose contained 20 to 30 hypophysectomized rat units. As this was considered a large dose for such small animals, the initial two injections were of 0.5 mg. each. The average injection period was 23 days. The number of growth hormone units injected daily was less than one-half that stated to have been injected daily by Salmon.

The method of thyroidectomy, the characteristics of the thyroidectomized animals and method of determining completeness of the operation have been described in the preceding paper (Scow and Simpson, '45). Only animals with a skeletal age of 15 days, when chronologically 30 days old, were used in these experiments. The rats were divided into two equal groups, one to be injected with growth hormone and the other to act as a control group. The injection period began on the thirty-second day of age. (A preliminary report of this study has been given by Scow, '43 and by Scow and Marx, '44).

BODY WEIGHT

The increase in body weight of injected (11) and uninjected (7) rats is shown in table 1 and figure 1. The body weight of the injected rats doubled during the 23-day injection period. Body weights were recorded for 12 days after cessation of injection and no further growth occurred. This growth during injection represented an increase of 1.1 gm. daily above the rate of growth of controls. It will be noted that the initial body weight of the injected rats was less because the smaller rats were placed in the injected group. As can be seen in figure 1, the growth hormone produced a greater increase in body weight in a group of three rats which later were shown to have small fragments of thyroid tissue.

Figure 2 shows the individual growth curves of three completely thyroidectomized rats, two of which received their first injections on the fifty-first to fifty-eighth day of life. A marked increase in body weight was observed during the injection period, with plateauing of the growth curve occurring after the injection period was terminated. When a second period of injection was begun in these same animals at 81 to 89

² When injected into hypophysectomized 26-28-day-old rats, 14 days postoperatively, in a total dose of 2.5 mg. over a 4-day period, the preparation (pH XXXI, 1c) showed no evidence of gonadotropic or adrenocorticotrophic hormones, while the presence of a trace of thyrotropic hormone was problematical. At a total dose of 5 mg. the presence of thyrotropic hormone was shown by a slight but definite response, and contamination by a minute amount of adrenocorticotrophic hormone became apparent. Such preparations are always found to have less than 0.5% lactogenic hormone.

TABLE 1

*The effect of growth hormone upon rats thyroidectomized at birth.
Daily injections of 1.0 mg. of growth hormone were made from the 32nd day of age for 23 days.*

Effect on body weight

TREATMENT	NO. OF RATS	BODY WEIGHT GAIN, GM.				
		During injection ¹			During 12 days following injection	
		Total	Daily	Per cent of body weight	Total weight gained	Weight gained per da.
Injected	11	35	1.4	100	— 2	— 0.2
Uninjected	7	7	0.3	17	4	0.3

Effect on skeletal growth and differentiation

TREATMENT	NO. OF RATS	LENGTH OF TIBIAL DIAPHYSIS, MM.		SKELETAL AGE, DAYS		
		Increase during injection period ¹	Increase during next 12 days	During injection		12 days after injection
				Onset	End	
Injected	11	6.6	0.7	15	18	18
Uninjected	6	4.8	0.7	15	18	18

¹ The value given for "injection period" included the two days subsequent to the cessation of the daily injections of growth hormone.

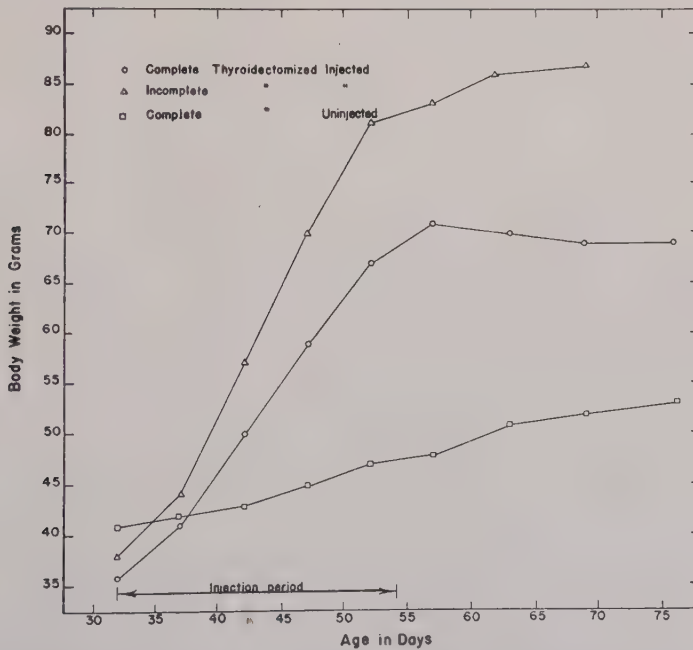


Fig. 1 Increase in body weight of eleven growth hormone injected and seven uninjected thyroidectomized rats during a 23-day experimental period beginning at 32 days of age. The body weight increase of three injected rats subsequently found to have been incompletely thyroidectomized is also shown.

days of age, they immediately displayed an increment of body weight, which again ceased when the injections were no longer given. A third rat was injected only during the second period, beginning at 89 days of age, at which time it was able to respond to the growth hormone.

Skeletal development. The roentgenograms³ showed that the increase in body weight was not due to a response of the soft tissue only, but also to an increase in the skeletal structure of the thyroidectomized rats.

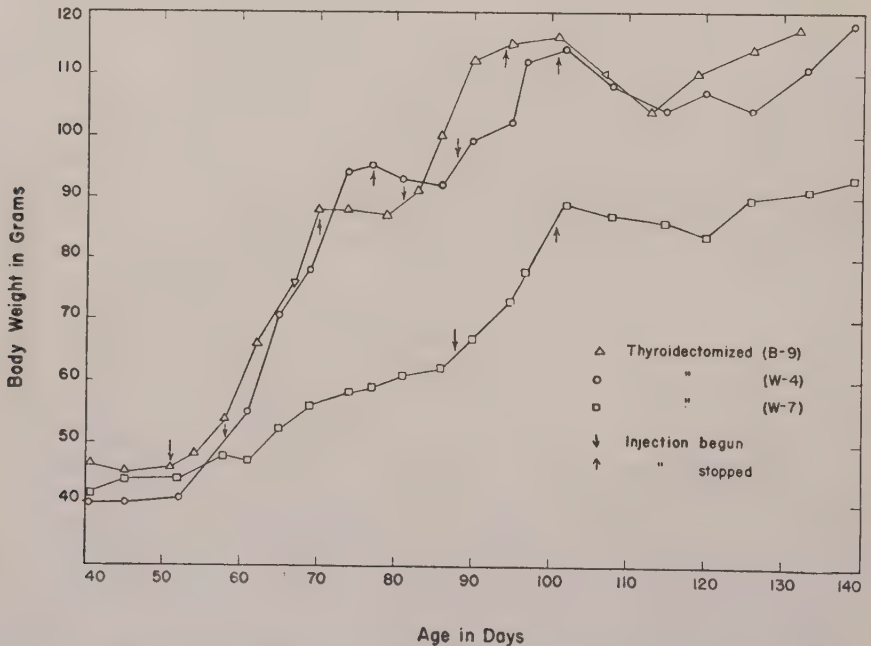


Fig. 2 Increase in body weight of two completely thyroidectomized rats injected with growth hormone for 18 days beginning on the fifty-first to fifty-eighth day of life, and again for 12 days beginning at 81 to 89 days of life. A third rat was injected only during the second period.

The response of the skeletal structures to growth hormone is recorded in table 1 and figure 3. The length of the diaphysis of the tibia was used as an index of the growth of the skeletal system. The increment in the length of the tibias of the injected rats during this period was 37% greater than that of the uninjected animals. During the 14 days after the injection period, the increase in the length of the tibia was about the same in both groups. It is noteworthy that though the bones did increase in dimensions, the shape of the bone was not altered. No

³ Roentgenograms were made one before the injection period, one 2-4 days after the injection period, and one just prior to autopsy.

changes were noted in the number of tarsal and carpal bones, or in the shape of the ends of the diaphyses, and the epiphyses. This is a most remarkable effect of the growth hormone upon the skeletal system, namely, to stimulate the growth in size of the bony structures without the accompanying appearance of new epiphyseal centers. The skeletal

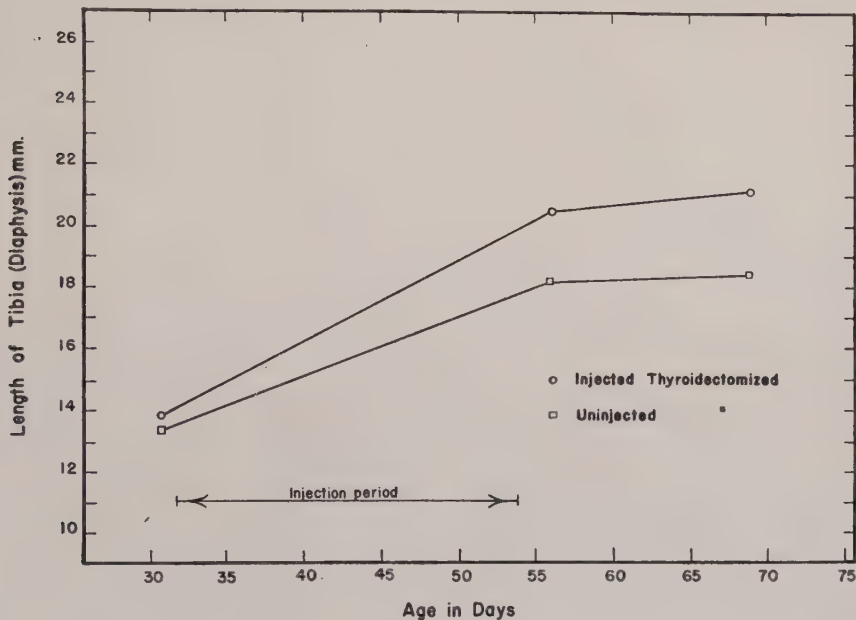


Fig. 3 Increase in the length of the tibial diaphysis (measured by roentgenogram) of eleven completely thyroidectomized rats injected with growth hormone and six uninjected controls.

age of the injected rats was the same as that of the uninjected rats of the same chronological age. Similar effects upon the skeletal structures were observed in the rats injected at the older ages (fig. 4).

Typical roentgenograms illustrating the effect of growth hormone upon the skeletal system are shown in figures 5-8. The uninjected thyroidectomized rat in figure 5 has a chronological age of 89 days, but a skeletal age of only 18 days, as may be seen by comparison with the normal 18-day-old rat in figure 7. The slightly greater width of the ends of the diaphyses in the thyroidectomized rat is the only noticeable difference. The effect of growth hormone upon the skeletal system of the thyroidectomized rat is shown in figure 6. The animal is a littermate of the uninjected rat in figure 5, but was injected with 1 mg. of growth hormone daily for 22 days, beginning at 30 days of age. Although the bones have increased in dimensions, the degree of ossification has re-

mained the same as that of the 18-day-old normal rat. For comparison, a normal rat of the same chronological age, 89 days, is shown in figure 8.

Other observations. No acceleration in the opening of the vagina, or changes in the gonads or adrenals were observed. The peculiar gait was unaffected by the injection of growth hormone as was also the transformation from the infantile hair to the adult hair. The weights of the organs and the ratio of these weights to body weight, as shown in tables 1 and 2 of the preceding paper, were unaffected.

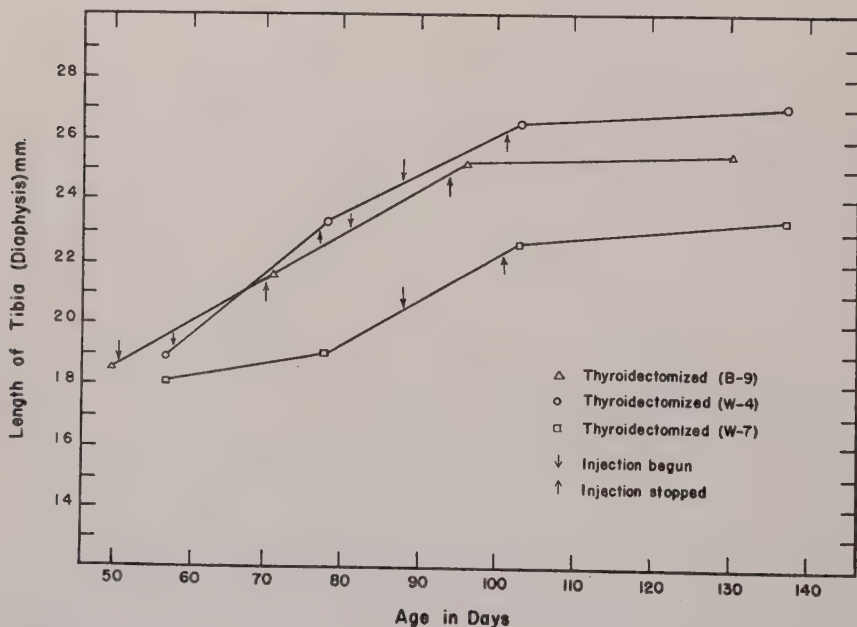


Fig. 4 Increase in the length of the tibial diaphysis of the completely thyroidectomized rats shown in figure 2.

DISCUSSION

It has been clearly shown by this experiment that the administration of a purified growth hormone preparation of the anterior pituitary gland for a period of 23 days will cause a marked increase in the body weight and in the size of the skeletal system of the rat thyroidectomized at birth. This is in agreement with the effects of growth hormone upon rats which were deprived, at weaning age or later, of their pituitary or thyroid gland, or both glands.

According to these findings, the age at the time the thyroid gland is removed is not a crucial factor in determining whether or not growth can be elicited by the injections of growth hormone. Furthermore the length of time after the operation does not seem important since the

stimulation of growth could be initiated in these dwarfs as early as 29 days and as late as 89 days of age.

In discussing the possible reason for the failure of Salmon to obtain growth following the administration of growth extract to thyroidectomized rats, the state of the health of these animals must be considered. It was pointed out in the preceding paper that marked differences existed in the characteristics after 23 days of age between the thyroidectomized rats reared by Salmon and those described here. In the former case a growth plateau was reached at 23 days, the rats were susceptible to intestinal disturbances and infection, and had a maximal longevity of 60 days. Further, Salmon injected "only those rats which ceased growing after 23 days" of age. A very slow prolonged growth is described here as characteristic of the rat considered completely thyroidectomized by all the criteria used (see preceding paper). It is possible that the rats reared by Salmon which "ceased growth" at 23 days of age were incapable of growing when stimulated by growth hormone. This remark has been occasioned by the observation that animals in the present series which were suffering from mild intestinal disturbances, such as flatulence, were not able to respond to the growth hormone and frequently became worse until the injections ceased.

Smith, Evans, and others have shown that the response of animals to growth hormone is greater when thyroid hormone is present. This was clearly shown in this experiment, since the response of the animals shown to have small fragments of thyroid tissue was greater than that of those which were completely thyroidectomized.

CONCLUSIONS

1. The growth rate of rats completely thyroidectomized at birth was stimulated by a purified preparation of anterior pituitary growth hormone. The following points were noted:

- a. The body weight was doubled in 22 days.
- b. The skeletal size increased at an accelerated rate.
- c. No acceleration was observed in the appearance of secondary ossification centers.
- d. The response elicited did not depend upon the age of the animal at the beginning of the injections of growth hormone.

2. The growth stimulating effect of growth hormone was greater in thyroidectomized rats which were shown to have a fragment of thyroid tissue present than in completely thyroidectomized rats.

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PLATE 1

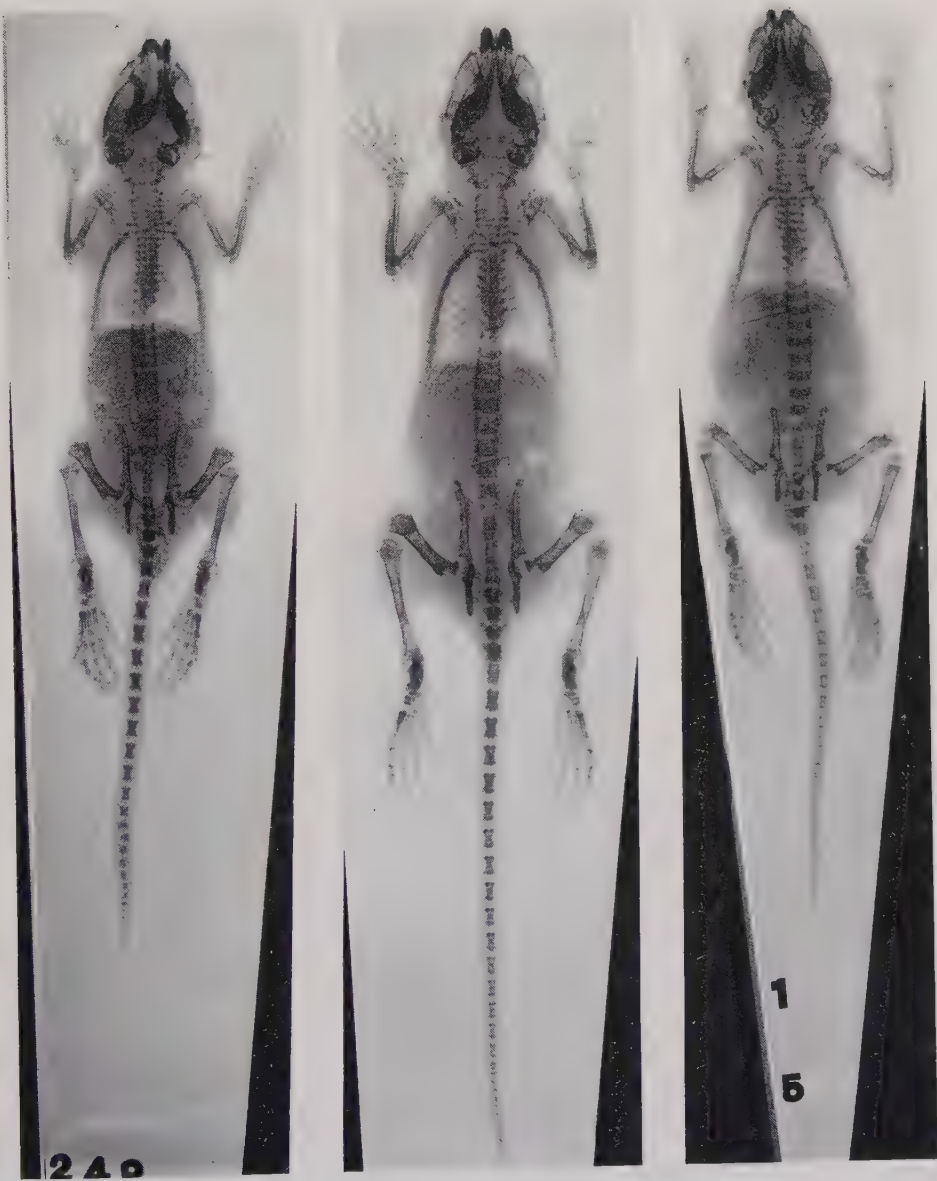
EXPLANATION OF FIGURES

Roentgenograms of normal and thyroidectomized rats, $\frac{2}{3}$ actual size.

5 Uninjected 89-day-old rat which was thyroidectomized on the first day of life. The skeletal age of this animal is 18 days, as may be seen by comparison with the 18-day-old normal rat in figure 7. Note the slightly wider ends of the diaphysis in the thyroidectomized rat.

6 Littermate, thyroidectomized on the first day of life, of the rat shown in figure 5; injected with 1 mg. of growth hormone daily for 22 days, beginning at 30 days of age. The rat gained 41 gm. during the injection period. Whereas the bones have increased in length and breadth, there has been no advance in skeletal age, as may be seen by comparison with the 18-day-old normal rat in figure 7 and the 89-day-old normal rat in figure 8.

7 Normal 18-day-old rat, with which the skeletal development of the 89-day-old thyroidectomized rats in figures 5 and 6 is to be compared.





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8 Roentgenogram of a normal 89-day-old rat, $\frac{2}{3}$ actual size. The skeletal development is far in advance of that attained by thyroidectomized rats of the same chronological age (figs. 5 and 6).

A NOTE ON THE RELATIVELY HIGH NUMBER OF ARGENTAFFIN CELLS IN THE MUCOSA OF THE HUMAN STOMACH

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ONE PLATE (FIVE FIGURES)

In textbooks of histology there are only very general statements regarding the presence and numbers of argentaffin cells in the human stomach. “. . . the argentaffin cells are only occasionally present in the stomach” (Bremer and Weatherford, '44, p. 339). “Argentaffine cells have been observed occasionally in the gastric glands;¹ they are somewhat more frequent in the cardiac and pyloric glands” (Maximow and Bloom, '42, p. 401). “In the stomach enterochromaffin cells are comparatively rare but do occur in the pyloric as well as in the gastric glands, rarely in the cardiac glands” (Cowdry, '34, p. 282). It is difficult to find full justification for these general statements from an examination of the literature or to gain any quantitative measure of such terms as “rarely” and “occasionally.”

There has been divergence of opinion on the presence of argentaffin cells in the human stomach especially among the more recent investigators. Kull ('25) apparently only noted basal granular cells in ectopic intestinal tissue of the pylorus but found none in the true gastric mucosa. Hamperl ('25) appears to be the most frequently quoted author but in his work his attention was apparently directed chiefly to the intestine and his data on the stomach are very scanty. He is responsible for the statement that argentaffin cells cannot be demonstrated in tissue obtained by autopsy later than 4 or 5 hours after death. However, in a later paper Hamperl ('27) made a careful study of tissues from fifty-eight human stomachs and concluded that there was a direct correlation between the number of argentaffin cells and the de-

¹ Many authors use the term gastric gland in a restricted sense to include only those glands which possess both parietal and zymogenic cells and are thereby distinguished from cardiac and pyloric glands. Others, perhaps inappropriately although not less logically, use the term fundic gland as a synonym for gastric gland. In the present paper fundic gland will be regarded as the equivalent of gastric gland as defined above and the term fundus will be used to include all areas of the mucosa of the stomach that contain fundic (gastric) glands. The terminology is far from satisfactory.

gree of pathological modification present. The cells were absent or rare in the normal tissues and numerous in intestinal-like areas and in "pseudopyloric" glands of the gastric mucosa. Friedmann ('34) appears to agree that there are none or only few argentaffin cells in the normal gastric mucosa of man. Jacobson ('39), in discussing these cells, states: "they occur in the cardiac region, are practically absent in the fundus¹ and are always found in fair numbers in the pyloric region."

Gillman ('42) states that the basal granular cell is restricted exclusively to the mucosa of the small and large intestine since he could find no argentaffin cells in the human (Bantu) stomach even after repeated examinations of ten stomachs, from cardia to pylorus. The Bantu tissues were removed almost immediately after death due to violent trauma, and fixed in formol. The sections were impregnated with silver according to the method recommended by Masson. Popoff ('39) illustrates (fig. 8B) numerous argentaffin cells in the human stomach without comment in the text or description of the region of the stomach from which the tissue was obtained. He used a special method of silver impregnation, the selectivity of which is questionable.

Argentaffin cells have also been reported as absent or nearly absent in the fundus of the rat (Jacobson, '39) and guinea pig (Jacobson, '39; Gillman, '42). However, Dawson ('44) found a great number of these cells in the stomach of the rat. He used a slight modification of Bodian's protargol technique (Dawson and Barnett, '44), the cells appearing black on a golden-yellow background. I also have found no difficulty in demonstrating these cells in the stomach of the guinea pig. The Bodian method appears to impregnate selectively cells which other investigators have failed to demonstrate adequately with other methods. In recognition of this, the Bodian technique was applied to the human stomach in hope of obtaining results similar to those in the rat and guinea pig.

MATERIALS AND METHODS

Human tissue used in this work was fixed in Bodian's formol-acetic acid-alcohol fixative and cut at 7 micra. All tissues were obtained after surgical removal or within 6 hours of death, with the exception of one piece of tissue fixed 18 hours postmortem. Four to five hours has been reported as the time limit for the persistence of argentaffin cells after death (Hamperl, '25). However, this was not found to be the case in the present study, since there was no direct evidence of the disappearance of these cells from any of the tissues examined. Tissue from the fundic (two specimens) and pyloric (one specimen) regions of the

stomach and the upper duodenum (one specimen) were examined for the number, form and distribution of argentaffin cells.

OBSERVATIONS

In the portion of upper duodenum studied (removed surgically) the argentaffin cells presented the classical picture so adequately described and illustrated in many papers. The cells were distributed throughout the epithelium of the intestinal crypts and villi. In most instances their granules were deeply blackened but occasionally slender cells containing only brown granules were observed. Only occasionally argentaffin cells were found in the glands of Brunner although Gillman ('42) apparently found them to be frequently present in the Bantu tissue.

The portion of pyloric stomach examined was also removed surgically. The pyloric glands appear normal in distribution and form. It is difficult to compare the relative numbers of cells present in this tissue with those of the duodenum and fundus since the epithelial patterns are so different. A few data will be given for the numbers counted in microscopic fields of the same magnification. However, it is realized that the pyloric glands are not so closely packed as are the fundic glands and that the pits of the pyloric glands reach deeper into the mucosa (over half-way). Furthermore the relatively short glands are coiled so that most of them are cut in transverse rather than in longitudinal section. The fundic glands, however, are usually much longer and are straight so that if the tissue block is properly oriented the glands are cut longitudinally.

The argentaffin cells are absent from the epithelium of the pyloric foveolae but are relatively numerous in that of the glands proper. Random counts from five microscopic fields at 450 diameters (Zeiss objective $\times 20$, binocular body $\times 1.5$ and ocular $\times 15$) show a range in number 12, 14, 17, 18, 23 to 28 cells per field. The basal zone of the pyloric mucosa in which argentaffin cells are found is relatively narrow, barely of sufficient width to fill the field of the microscope at 450 diameters. On the other hand there is a much wider zone of argentaffin cells in the fundic mucosa, so that, while the density of distribution in the pyloric mucosa per microscopic field may be almost comparable to that of the fundic tissue the total number of cells per square millimeter of surface area is much less. The pyloric argentaffin cells are usually intraepithelial in position; that is, they extend into the epithelium for varying depths, intruding between the typical pyloric cells. Many appear as long wedges reaching the lumen, while others may not extend so far and approximate equilateral triangles in outline.

Most of the cells are well granulated and the granules commonly occupy the entire cytoplasm. They are seldom restricted to a basal location.

The epithelium glands of the fundic region of the human stomach contain a relatively large number of argentaffin cells which tend to be concentrated in the inner third of the mucosa. However, they also occur more diffusely in the middle third but only occasionally is an argentaffin cell found near the foveolae. In tissue taken 18 hours after death the mucosa shows evidence of cellular dissociation especially in the foveolae, and in adjoining regions where the parietal cells are most numerous (fig. 2). In the deeper lying zone in which zymogenic, chief cells predominate the preservation is remarkably good (fig. 3). Random counts of argentaffin cells from five microscopic fields ($\times 450$) give the following values: 17, 18, 21, 16 and 26. However, it was not always possible to determine the exact relationships of the argentaffin cells to the glandular epithelium. In this tissue the zone of argentaffin cells was two fields wide.

In the other specimen which was obtained at an early autopsy (slightly less than 6 hours after death) the histological preservation was excellent. The piece of tissue was somewhat distorted and accordingly the plane of the sections did not pass vertically through the fundic glands of the entire sections. The thickness of the mucosa appeared greater than that of the other specimen obtained postmortem so that the zone of argentaffin cells frequently was three microscopic fields ($\times 450$) in width. The counts per field were also higher; perhaps due to the slight obliquity of the sections or to the different locations in the stomach from which the two tissues were removed. Counts of argentaffin cells in five fields selected at random were as follows: 31, 21, 23, 27, and 32. The general pattern of their distribution and their density of distribution is adequately illustrated in figure 1.

The form and position of the argentaffin cells of the fundus is extremely variable. Some are triangular or rounded and lie in the epithelium. Others are flattened and irregular in outline and lie almost external to the tubule or occupy what is spoken of as a periglandular position (figs. 4 and 5). Frequently granular processes of varying lengths are insinuated between the cells of the tubule wall. The cells are small; seldom as large as the body chief cells and always smaller than the parietal cells. The granulation is usually very dense and the granules completely fill the cell.

The demonstration of relatively large numbers of argentaffin cells in the human stomach not only in the pyloric glands but in the fundic glands as well is interesting not only in regard to the question of their

absence or relative absence from the fundus as reported recently, but for the light it throws on the possible function of these cells. Jacobson ('39) connected them with the elaboration of the anti-anemic factor (intrinsic factor of Castle). One of the main premises on which he based this conclusion was the correlation he observed between the distribution of argentaffin cells and the presence of the anti-anemic factor; he found them both only in the cardiac and pyloric regions of the stomach.

The situation in the human stomach seems quite like that of other mammals (Dawson, '45) in which the number of argentaffin cells is high in the fundic region with fewer cells in the pyloric tissue.

SUMMARY

A modification of the Bodian protargol method was used to demonstrate the presence of argentaffin cells in both the fundic and pyloric glands of the human stomach. This method also shows these cells to be present in the duodenum in the typical form and pattern revealed by other silver techniques, such as Masson-Hamperl. It does not seem possible to employ longer the terms "rare" or "occasional" in discussing the occurrence of argentaffin cells in the human stomach. From the limited material examined it is concluded that the population of argentaffin cells per square millimeter of stomach surface is much higher in the fundic than in the pyloric regions.

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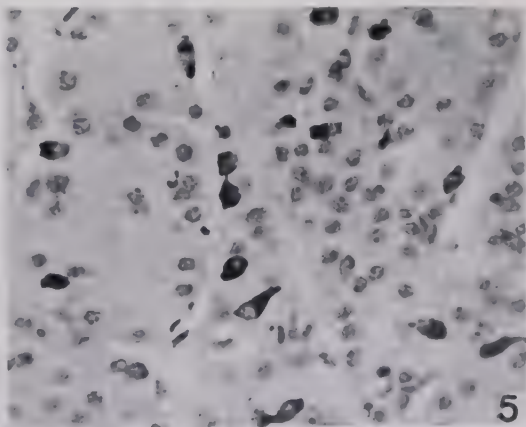
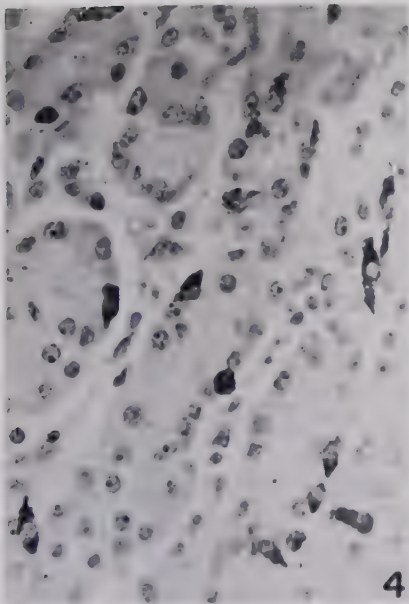
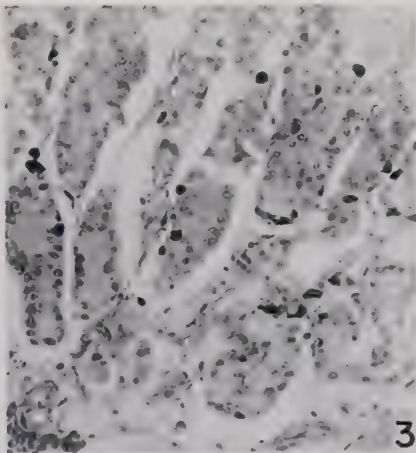
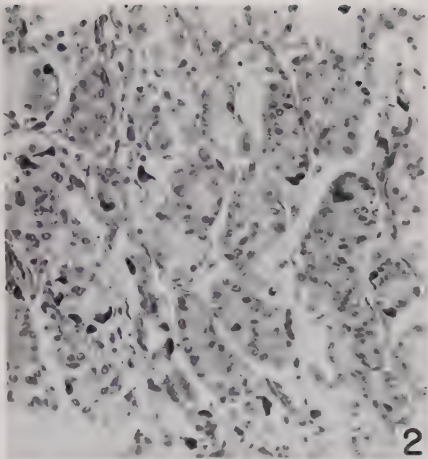
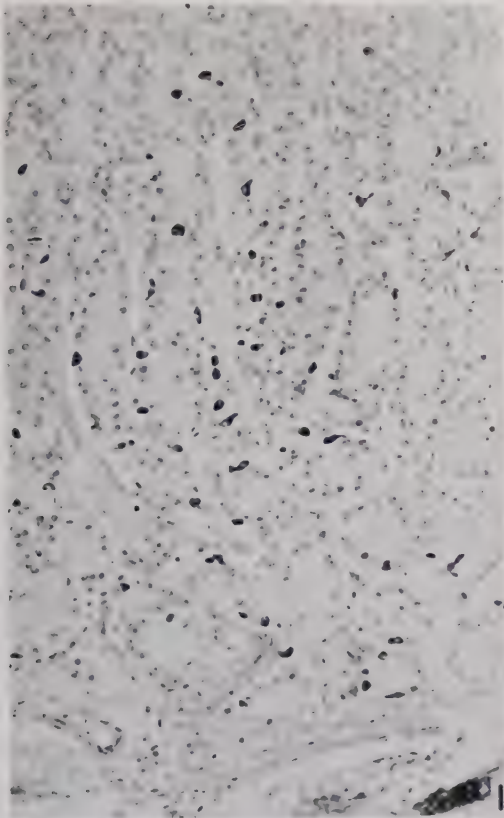
EXPLANATION OF PLATE

All figures are photomicrographs taken at the magnifications indicated below. All tissues are of adult, human stomach, prepared according to a modification of Bodian's protargol method, without gold toning. All sections were cut 7 micra thick.

PLATE 1

EXPLANATION OF FIGURES

- 1 Vertical section of the fundic mucosa showing the number, form and distribution of the argentaffin cells. The basal zone illustrated is the region of greatest concentration of these cells. Superficial to this the cells are relatively few and scattered. Tissue obtained from an early autopsy, less than 6 hours after death. $\times 200$.
- 2 Vertical section showing the number and distribution of argentaffin cells in the middle third of the gastric mucosa. Parietal cells are present but the body chief are more numerous. The tissue was obtained 18 hours after death and postmortem cytolysis is evident. $\times 225$.
- 3 Vertical section through the basal zone of the fundic mucosa from the same tissue as shown in figure 2. Many of the argentaffin cells appear rounded and some are dissociated from the glandular epithelium. $\times 225$.
- 4 and 5 Two basal regions from the same tissue as illustrated in figure 1 showing the form and position of the argentaffin cells. $\times 450$.



ABORTIVE PARTHENOGENESIS IN THE DOMESTIC CHICKEN

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ONE PLATE (SIX FIGURES)

As yet, the question of parthenogenesis in the domestic fowl (*Gallus gallus*) has not been properly settled. Oellacher (1872) answered the question in the affirmative, Lau (1894) and Barfurth (1895) in the negative. The matter then remained in abeyance until Lécaillon, in a series of papers published between 1908 and 1910, reconsidered the problem and concluded that the unfertilized hen's ovum undergoes a form of parthenogenetic cleavage. (His memoir of 1910, cited in the bibliography, lists the series in full.) Lillie in the second edition of his book, *The Development of the Chick* ('19), makes no reference to Lécaillon's work. He cites, however, the already mentioned paper of Barfurth in the bibliography of the book and states that "the so-called parthenogenetic cleavage of such eggs (i.e. infertile eggs. I.L.K.) is merely a phenomenon of fragmentation of the protoplasm. There is no true cell-division". Bartelmez and Riddle ('25) found evidence of parthenogenesis in the pigeon.

The purpose of the present paper is to re-open the subject in the light of the more recently developed histochemical techniques which aid in the interpretation of strictly morphological data.

MATERIALS AND METHODS

Freshly laid, unincubated eggs, of either virgin or non-mated Barred Rock and White Leghorn hens, provided the necessary material. In case of the non-mated group, hens had been isolated from males for at least 60 days as, according to Barfurth (loc. cit.), "Nach dem vierzigsten Tage der Isolierung vom Hahn, gelegte Eier sind sicher unbefruchtet". All yolks were fixed within 1-3 hours of oviposition, because experience has shown that the histological picture of the infertile egg degenerates rapidly after laying. Fixation was carried out either in Zenker's fluid or the sublimate-acetic acid fixative (Lee, '37). Following that, the blastodisc was removed from the yolk, dehydrated in a 50-50

mixture of paraffin and Fisher's tissuemat and sectioned serially at 7-8 μ . In most cases the material was sectioned tangentially, although some vertically sectioned preparations were made. Of the some 100 blastodiscs sectioned, half were stained with Delafield's hematoxylin and eosin; the other half was subjected to Feulgen's histochemical test for desoxyribonucleotides. The test was found extremely useful in locating mitotic figures. After some experimentation, Grüber's basic fuchsin was found to give the most consistently satisfactory results.

RESULTS

The examination of sectioned blastodiscs has revealed the presence of nuclei, both intact ("resting") and mitotic. The frequency with which the nuclei appeared varied inversely with the post-oviposition age of the egg. The nuclei were most numerous in the blastodiscs of eggs fixed within 3 hours of laying; about 25% of the blastomeres of such eggs were found to contain nuclei, while by the twenty-fourth hour, the nuclei were almost non-existent.

Both methods of treatment adopted in this study have revealed the presence of nuclei. With the haematoxylin-eosin technique, most of the intact nuclei were stained uniformly dull blue (fig. 1). Each nucleus contained one or two nucleoli, as do normally proliferating embryonic chick cells; only a few of these cells possessed vesiculated nuclei, in contrast to the nuclei of "normal" embryonic chick cells which are extremely vesiculated. The mitotic nuclei were rare; only 16% of the examined blastodiscs contained such nuclei, the average being two per blastodisc, with the maximum of four. Some mitoses were multipolar (fig. 2).

The Feulgen test produced interestingly parallel results. Only few nuclei responded with a positive reaction, the great majority being entirely negative. These appeared as "ghost" bodies. The reaction produced by the intact nuclei was less striking than that of the mitotic nuclei, although color intensity in the former was sufficiently great to reveal their vesicular nature. Chromosomes of the dividing cell give a strongly positive Feulgen reaction (figs. 3 and 4) in contrast to a negative reaction in the cyto- and nucleoplasm. In fact, generally the reaction was so clear cut, that the infrequently occurring mitoses could be easily located under a low power microscope. The invariable presence of a granule-free area around the mitosis was of great help in this regard.

In addition to the already described types of nuclei, there was another, frequently encountered, nuclear form which deserves a brief

mention. These were nuclei in the various stages of fragmentation (figs. 5 and 6). The first of the two examples shows a nucleus, Feulgen negative except in the central portion, ready to break up into several fragments. The other example is that of an already fragmented nucleus.

DISCUSSION

Evidence collected from the material on hand points strongly to the existence of abortive parthenogenesis in the unfertilized eggs of the domestic fowl. The process is "abortive", in contrast to the "functional" parthenogenesis of many lower forms. Kampmeier ('29) defined "true" parthenogenesis as "the orderly development of a mature unfertilized ovum by regular cleavage into an independent individual, or at least into the fundamentals of such an organism". He concluded that the evidence offered for the occurrence of such parthenogenesis, at least in the mammals, is "extremely scanty". On the other hand, a different interpretation might be offered, if the phenomenon of parthenogenesis is interpreted to mean merely the development of an egg without fertilization. If the latter interpretation is accepted, then there is considerable evidence for the existence of gynogenesis in higher forms (Newman, '13; Loeb, '15 and '32; Häggström, '22; Krafka, '39; Reimann and Miller, '39). It is in this sense that the unfertilized chicken ovum undergoes parthenogenesis. The process is extremely brief, terminating soon after oviposition. It can not be revived by incubation. The maternal cells of such ova are capable of division by means of apparently normal mitoses (although the presence of multipolar karyokinesis is not ruled out). The shape, the size and the number of chromosomes involved, leave no doubt as to the nature of these divisions. Furthermore, the fact that more than one, and in one case as many as four mitoses were observed in one blastodisc, adds weight to this interpretation. Precautions taken in the present study to assure true infertility were sufficiently stringent to avoid any criticism of the results on this score. One of the strongest objections to Oellacher's work raised by Lau and Barfurth (*loc. cit.*), dealt with the matter of apparent and true infertility. The diploid chromosomal complement observed in the mitotic nuclei can be plausibly accounted for by assuming that in the hen, as in many lower forms (Tyler, '41), expulsion of the second polar body is predicated upon fertilization. Lillie (*loc. cit.*) considered this as a possibility: "It seems probable that (in the hen. I.L.K.), as in many other animals, the completion of maturation is dependent on the stimulus of fertilization." Olsen ('42) pointed out that

in the hen "the second polar body is extruded following the penetration of the sperm".

The infrequency with which mitoses occur in the blastodiscs of infertile eggs suggests that the developmental potential of such blastodiscs is low. It is probable that the bulk of the visible nuclei, which stain dull blue with haematoxylin or are Feulgen negative, are moribund or dead. The few which are still alive respond to the Feulgen reagent with a reaction, the degree of which depends upon the physiological state of the individual nucleus. The most intense response is given by the actively dividing nuclei i.e., the nuclei which are still in possession of a dynamic potential and thus capable of synthesizing the essential nucleoproteins. This is in line with the modern concepts of metabolic changes in a living nucleus.

SUMMARY

Results secured from the study of some 100 blastodiscs of eggs laid either by non-mated or virgin hens indicate the existence of abortive parthenogenesis in the domestic chicken. The process is of short duration and can be demonstrated in about 15% of such blastodiscs by the application of the Feulgen test.

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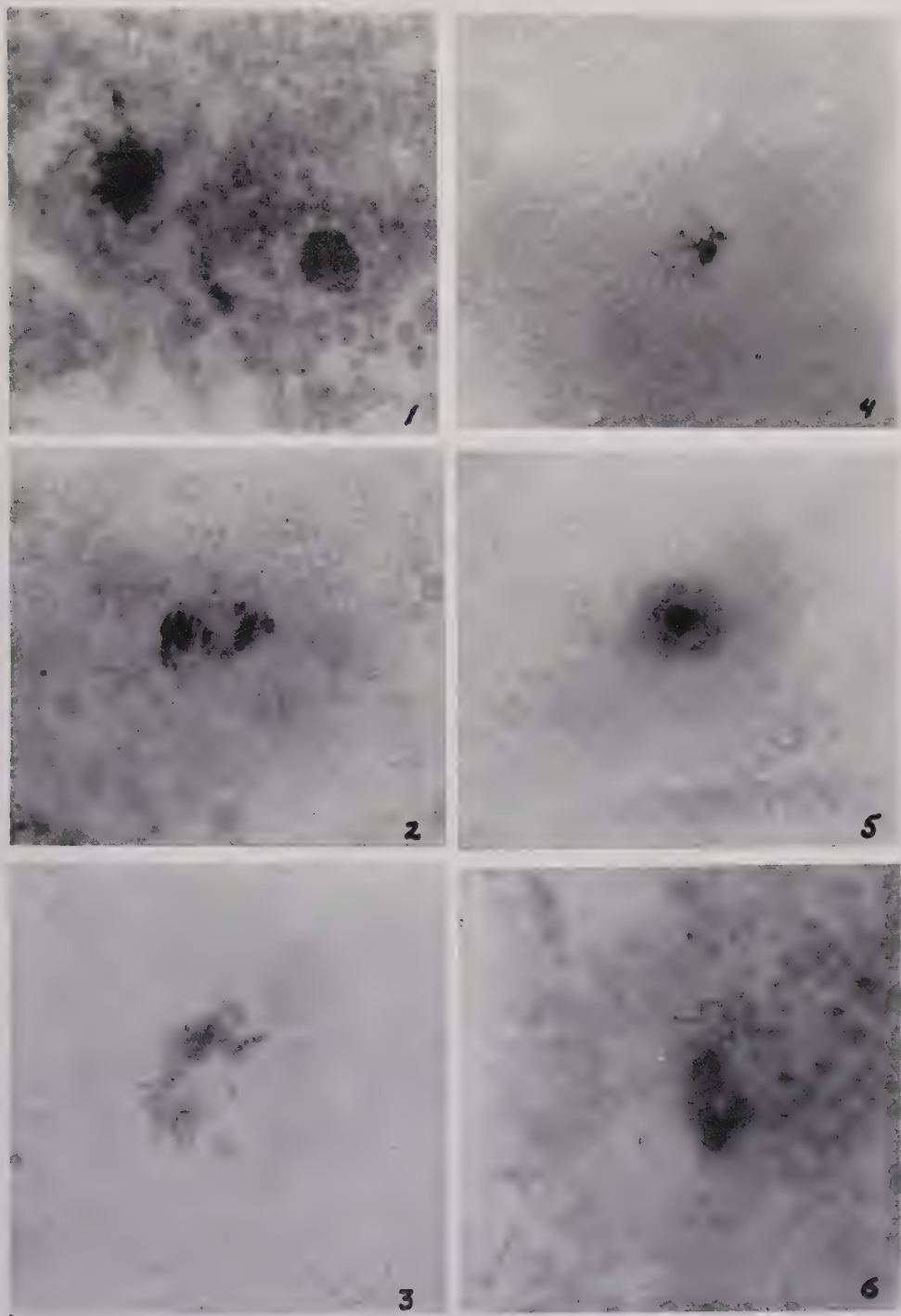
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PLATE 1

EXPLANATION OF FIGURES

- 1 Two nuclei in the blastodisc of an egg laid by a non-mated hen. The top nucleus is commencing to break up. Haematoxylin-eosin.
 - 2 A bipolar mitosis. Virgin hen. Feulgen test.
 - 3 Polar view of metaphase. This particular blastodisc had four visible mitoses. Virgin hen. Feulgen test.
 - 4 Another example of mitosis in the blastodisc of an infertile egg. Non-mated hen. Feulgen test.
 - 5 and 6 Two nuclei in the process of breaking up. Virgin hen. Feulgen test.
- Magnification: $\times 1400$.



AN ABNORMAL HEART IN RANA PAPIENS

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TWO FIGURES

The heart here described seems of sufficient interest to merit a short account. It was found in a fully mature female killed for class use along with a number of others, and no external peculiarities were observed. When the ventral skin was opened, what appeared to be the ventricle of the heart was seen dorsal to the anterior edge of the pectoral muscles and ventral to the submaxillary muscles of the right side; removal of the sternum and associated structures revealed a heart with the general relations shown in figure 1.

About one-third of the ventricle projected beyond the front end of the sternum, and the ventricle as a whole lay entirely to the right of the sagittal plane between the line of the right sternohyoid muscle and the jaw.

The atrium lay posterior to the ventricle and obliquely towards the middle line so that it passed dorsal to the right sternohyoid muscle, by which it was strongly constricted.

The sinus venosus was in the normal site and, in the undisturbed ventral view, was concealed by the atrium and the liver.

The liver lacked a cardiac fossa and had on the left lobe, which was very large, a shallow supplementary incisura. The ventral abdominal vein entered the liver at the usual place.

The submaxillary muscle on the right side was very thin, being for the most part reduced to a mere sheet of fascia.

The heart was enclosed in a thin membrane (not shown in the sketch), which is presumably pericardium. This was free over the ventral surface of the ventricle, but round the sides and on the dorsal surface it was firmly attached; it was also fused to the adjoining submaxillary fascia. It was firmly fused to most of the surface of the atrial region, and was particularly strongly attached to the fascia of the sternohyoid muscle where this crossed the atrial region. It was free over most of the sinus venosus. The truncus arteriosus was invisible in ventral view. (The term truncus is used for convenience without prejudice to the conus-bulbus question.)

Removal of the right sternohyoid muscle, and some further dissection, showed the sinus venosus, atrial region and ventricle to be morphologically in a nearly straight line, with the truncus directed posteriorly on the dorsal surface.

The heart, with the origins of the great vessels, was removed for more detailed examination, and its dorsal aspect is shown in figure 2.

The sinus venosus was as nearly normal as the unusual position of the atrial region allowed, and had normal relations to the pulmonary

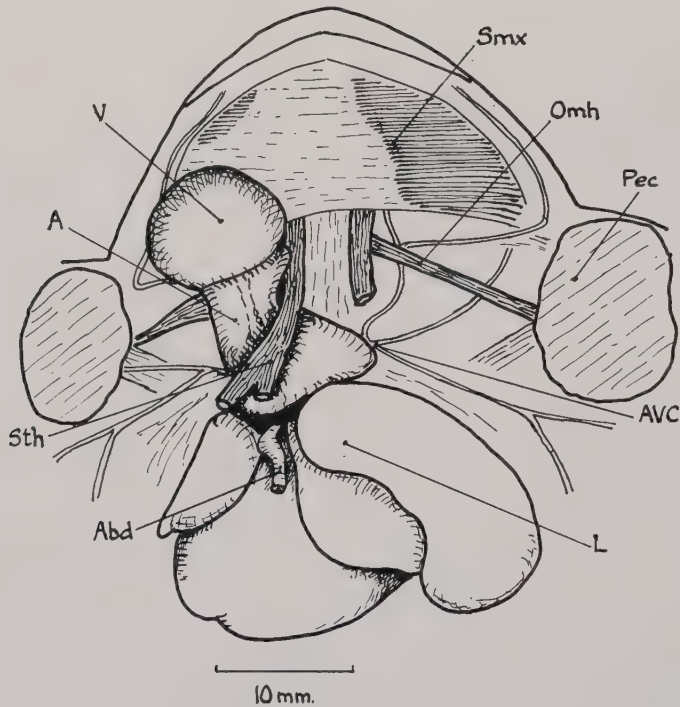


Fig. 1 General view of heart and adjacent structures after removal of pectoral body wall. A, atrial region; Abd, ventral abdominal vein; AVC, anterior vena cava; L, liver; Omh, omohyoid muscle; Pec, cut ends of pectoral muscles; Smx, submaxillary muscle; Sth, sternohyoid muscle; V, ventricle.

veins and to the cardiac branches of the vagus nerve. The ventricle was somewhat flattened dorso-ventrally and was markedly circular in outline, but was otherwise structurally normal. The atrial portion showed the greatest deviations, being an irregularly expanded tube connecting the sinus with the ventricle. The sulcus coronarius was well-defined and there was an indication of the sulcus longitudinalis on the ventral surface.

Internal features conform to the external findings. The sinus venosus had its endothelial folds normally developed in relation to the openings of the veins. The ventricle differed in no significant way from the normal structure. The atrial region showed as high a conformity with the norm as its unusual relations permitted. The right atrium was bigger than the left and lay partly dorsal to it. The internal features were less sharply marked than usual, though they could all be recognized, e.g., it was hard to determine precisely the limbus of Vieussens, the spatium intersepto-valvulare was not well-defined, and the muscle bundles in the walls were unusually diffuse.

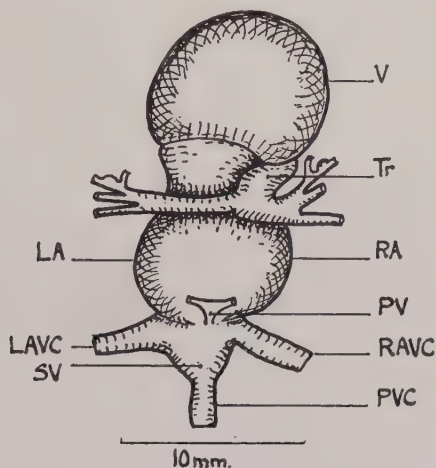


Fig. 2 Dorsal view of heart removed from body. La, left atrium; LAVC, left anterior vent cava; PV, pulmonary vein; PVC, posterior vena cava; RA, right atrium; RAVC, right anterior vena cava; SV, sinus venosus; Tr, truncus arteriosus; V, ventricle.

The truncus arteriosus left the right posterior corner of the ventricle and coursed obliquely backwards in a groove on the dorsal surface of the atrium; at about the usual level it divided into two normal branches lying in grooves in the atrial wall, and the branches had normal distributions to the various regions of the body.

It may be noted that except for the heart and a few immediately associated structures, e.g., submaxillary muscle, the specimen was normal.

DISCUSSION

This heart appears to be a striking example of persistent general embryonic conditions carried to an adult state of functional differentiation; it exhibits to a high degree the primordial relations of the regions of the embryonic heart. The sinus venosus retains its original

site with reference to the liver; it cannot do otherwise since it was anchored early in development. The branches of the truncus were also anchored at an early stage. Between these two points, the posterior and anterior limits of the primitive pericardium, the heart normally twists in the well-known fashion. The heart under discussion can well be interpreted as one in which the ventricle and the atrial region have retained primitive relations through growth of the ventricle forward below the anchorage of the truncus into the lax subdermal tissues of the submaxillary region. This process of necessity drew the truncus forward and forced it to lie on the dorsal surface, and at the same time permitted the atrium to retain its primitive position. The pericardium may be regarded as having been carried along with the growth of the ventricle. These modifications of development, unaccompanied by far-reaching attendant dislocations, are perhaps comparatively simple in a frog because of the small elongation of the neck region.

An easy effort of the imagination can convert this heart into one very like the normal by bending the ventricle and the greater part of the atrial region ventrally so as to bring the tip of the ventricle near the entrance of the posterior vena cava into the sinus venosus; this with the help of a little differential growth produces relations not essentially different from those of the ordinary frog's heart.

TWO CASES OF ACCESSORY GALL BLADDER IN THE RHESUS MONKEY, *MACACA MULATTA*

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Department of Biology, Brooklyn College, Brooklyn, New York

TWO FIGURES

The presence of accessory gall bladders in mammals has been reported as far back as the 9th century, and in many cases the relative frequency with which such anomalies have occurred, has been established. Thus, Boyden ('26) gives a thorough account of the formation and frequency of occurrence of an accessory gall bladder in the cat (1 out of 8), calf (1 out of 28), sheep (1 out of 85), pig (1 out of 198), and man (see below). This paper of Boyden's contains a critical review and bibliography on the subject. More recently, Levin and Boyden ('40) described and classified in great detail, several types of accessory gall bladders in the ungulates discovered in the descriptions of the old Hebrew orthodox laws governing the preparation of meat.

A survey of the literature indicates a very low frequency of occurrence of this anomaly among the primates. Thus, Ruch ('41) makes mention of only one reference, namely to a paper by Subba ('28) on a case of accessory (triplicate) gall bladder in the monkey, *Loris lydekkerianus*. On the basis of a survey of cases compiled from several medical colleges and hospitals, Boyden ('26) showed that, in man, out of a total of 19,000 cadavers and patients examined, only five authentic cases were reported. He further pointed out that up to that time not more than twenty such cases had appeared in the medical literature. However, since the introduction of the Graham-Cole method of visualizing the gall bladder in 1924, more cases have been presented, raising the total number to at least thirty-seven (Wilson, '39). Because of the still low incidence of this anomaly in primates, it has seemed desirable to report the occurrence of two instances of accessory gall bladder in a total of 158 rhesus monkeys dissected during laboratory routine in the mammalian anatomy course at Brooklyn College.

As Lineback ('33) points out, the normal gall bladder in the rhesus monkey "is a greatly-elongated, thin-walled sac which lies on the caudal surface of the central lobe" of the liver. As in man, the cystic duct

of the gall bladder joins the common hepatic duct near the portal fissure to form the common bile duct (Ductus Choledochus). The fundus of the gall bladder scarcely extends beyond the free border of the liver, and the entire organ is completely covered by the capsule of Glisson which keeps it from becoming pendulous.

In the two monkeys observed, both the larger and the accessory gall bladders appear to have been functional. Each was imbedded in the inferior surface of the right central lobe of the liver and was completely covered by the capsule of Glisson.

Case 1 (fig. 1). Here, the larger gall bladder was thin-walled and sac-like, measuring 30 mm. long and 18 mm. in maximum diameter when flattened. Its fundus was partially divided by a constriction in its wall on the left — the so-called “phrygian cap” or folded fundus — the most



Fig. 1 Caudal aspect of gall bladders and associated ducts, dissected free from liver. Hepatic and bile ducts are flattened out. $\times \frac{1}{2}$.

Abbreviations for figures 1 and 2: GB, gall bladder; AGB, accessory gall bladder; CD, cystic duct; HD, common hepatic duct; BD, common bile duct.

common anomaly of the human gall bladder (Boyden, '35). Its neck terminated in the cystic duct which passed backward and downward and joined the common hepatic duct to form the common bile duct. The cystic duct was 17 mm. in length. Near its point of origin, a smaller accessory gall bladder emptied into it. This accessory bladder, 18 mm. in length and 10 mm. in maximum diameter, did not appear to have any duct of its own but its external and internal structure was no different from that of its counterpart.

Case 2 (fig. 2). In this animal, the larger gall bladder was slightly smaller than that of the specimen described above; 27 mm. in length and 15 mm. in maximum diameter. It was embedded so deeply in the liver that its fundus was visible through the anterior face of the right central lobe. Its cystic duct showed a definite pattern of spiral and circular folds as it coursed downward to its junction with the common hepatic duct. When straightened, it measured 39 mm. The accessory

gall bladder was completely independent of the larger bladder. It measured 18 mm. long and 10 mm. wide and possessed its own cystic duct, 20 mm. in length, which was accompanied by a separate branch of the cystic artery. The cystic duct of the accessory gall bladder joined the common hepatic duct slightly anterior to the entrance of the main cystic duct.

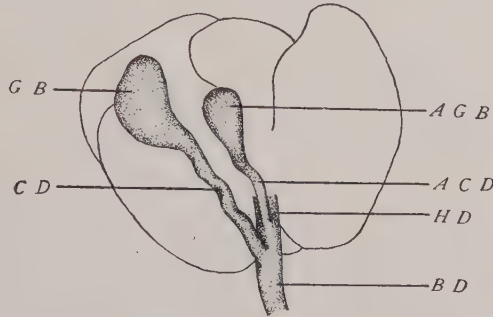


Fig. 2 Caudal aspect of gall bladders and associated ducts, dissected free from liver. Hepatic and bile ducts are flattened out. $\times \frac{1}{2}$.

DISCUSSION

Speculations as to the possible origin of the anomalies presented here should not prove necessarily difficult, particularly in view of the fact that similar cases have been studied and analyzed in other mammals. Thus, Boyden ('26) found four embryonic types of accessory gall bladder: (1) cleft gall bladder (chiefly in cats), forms which originate by initial subdivision of the primary cystic diverticulum of the embryo; (2) diverticular bladders (chiefly in ungulates), distinct vesicles or subordinate lobes, arising as buds from the neck of the embryonic gall bladder and usually associated with cyst-hepatic ducts; (3) ductular bladders (chiefly in man but also in cats), supernumerary vesicles derived from either hepatic, cystic, or common bile ducts; (4) trabecular bladders, vesicular outgrowths of liver trabeculae bordering the fossa vesicae felleae, rare anomalies found as yet only in cattle, sheep and possibly cats.

It is quite possible that the first anomaly presented here (fig. 1) arose as either: (1) a bud from the neck of the embryonic gall bladder (i.e., diverticular bladder), or (2) an initial subdivision of the primary cystic diverticulum of the embryo (i.e., cleft gall bladder). It is safer to classify the second of the two anomalies here reported (fig. 2). The presence of two distinct cystic ducts, in which the accessory duct leads into the hepatic duct before its union with the main cystic duct, indicates an origin from the hepatic duct itself; i.e., it is a ductular bladder.

SUMMARY

Two cases of accessory gall bladder anomalies in the rhesus monkey were discovered during routine laboratory dissection. In one of these cases, the accessory gall bladder was attached near the origin of the main cystic duct. It may have arisen either as a bud from the neck of the embryonic gall bladder, or, and this is more likely, from an initial subdivision of the primary cystic diverticulum of the embryo. In the second case, the accessory gall bladder and its duct was entirely independent of the main gall bladder, indicating its origin as an outgrowth from the common hepatic duct itself.

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BOOK REVIEW

EDGAR ALLEN MEMORIAL NUMBER OF THE YALE JOURNAL OF BIOLOGY AND MEDICINE. October, 1944, vol. 17, pp. 1-349.

"This number is dedicated to the memory of Edgar Allen, Professor of Anatomy and Chairman of the Department of Anatomy at Yale University School of Medicine, who died February 3, 1943, while performing duties in the service of his country." It contains his portrait, certain biographical data, a list of his publications and a series of twenty-seven papers by some of those investigators who were closely associated with him. Its publication was aided by a grant from The Jane Coffin Childs Memorial Fund for Medical Research.

Seventeen of the papers in his honor deal with problems in the field of endocrinology. Five of them present studies on estrogenic hormones — the bio-assay of β -estradiol, the action of estrogen on avian pigmentophores, the leukemogenic action of estrogen, the tolerance of estrogen by pregnant monkeys and the origin of mammary carcinomas in response to estrogen. Three are on androgens — the effect of synthetic androgens on spermatogenesis in hypophysectomized monkeys, the secretion of androgen by testes that are confined to the abdominal cavity and the effect of testosterone propionate on the structure of the anterior hypophysis. Four report the effects of various steroid hormones (on lactation, on the vaginal smear, on the oviduct of pigeons and on the nuclei of the cells of the endometrial stroma). One paper deals with the function of chorionic gonadotrophin and includes a speculative discussion of hormonal interrelationships in pregnant monkeys. Another paper presents observations concerning the effect of light (of different wave lengths) on the hypophysis. There is a preliminary note on the adreno-cortico-mimetic action of the ovary. There are two papers concerning thyroxin — the rate of secretion by the avian thyroid and the effect of hypothyroidism on menstruation.

Five papers are on neoplasms — recent studies on experimental mammalian leukemia, the influence of the age of recipient (mouse) on the carcinogenic action of methylcholanthrene, the susceptibility and resistance to cancer in mouse and man, the incubation period of cancer in man and the growth of transplanted lymphosarcoma in the mouse.

The five remaining papers need not be classified. The subjects are: the growth and development of the pelvis in girls; the pigmentation of the gonads after vitamin-E deficiency; the variation of electric potentials during estrus, ovulation and pregnancy; the effect of sex-linked genes on the "expression" of melanophores; and, "the magnification of the frontal writing lever."

Edgar Allen's publications were numerous (147 titles). Approximately two-thirds of them appeared under joint authorship, thus reflecting his enthusiasm — "human dynamo" that he was — for team work in research.

In his first publication, full of unanswered questions, he concluded that the cause of estrus could be narrowed down to the presence of large ovarian follicles.

However, he almost reached the erroneous decision that ova produce the hormone which will always be associated with his name.

When 31, he had already made two outstanding contributions. The story of the first is told by the opening sentence of an abstract of the paper which he presented before the American Association of Anatomists in 1923. It reads, "New formations of ova from the germinal epithelium of the mouse ovary occur during sexual maturity."

The second outstanding contribution, with E. A. Doisy, was based upon a simple experiment — introducing liquor folliculi from hog ovaries into the circulation of ovariectomized mice. The result of this experiment, estrus within 48 hours, was convincing. The follicular hormone had been discovered. Many of our concepts regarding the physiology of human reproduction were formulated in the light of this discovery.

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Excessive demands by war necessities upon transportation facilities have again forced the omission of the regular annual meeting of the Association. The 124 abstracts which follow may serve as a "spiritual" meeting, to use a term suggested by one of our members, while we all hope for an actual meeting in 1946.

Observations on pseudo-agglutination as seen in transparent chambers in living animals.

Richard G. ABELL and William M. PARKINS, Department of Anatomy and the Harrison Department of Surgical Research, University of Pennsylvania.

That gelatin causes erythrocytes to adhere in clumps, and increases sedimentation rate in vitro, is well known. The present studies were undertaken in order to determine whether such pseudo-agglutination occurs within the blood stream following intravenous injections, and whether obstructions to circulation of erythrocytes through arterioles capillaries and venules could be detected.

Six per cent solutions of intravenous gelatin (courtesy of Dr. D. Tourtellotte, Charles B. Knox Gelatine Co.) were infused into six rabbits and five dogs. In the dogs, the vessels were studied in transparent intestinal-mesenteric chambers (Zintel, '36). With normal rapid flow in the dog's mesentery no pseudo-agglutination could be detected following gelatin infusion. When circulation was markedly reduced by massive hemorrhage, clumping of erythrocytes occurred. Following replacement of the lost blood by an equal volume of gelatin, blood flow was promptly increased without detectable interference from pseudo-agglutinated cells. The clumps were readily dispersed as active circulation resumed.

Further studies were carried out by injecting gelatin intravenously into rabbits (15 cc./kg.) and observing the effects in transparent moat chambers (Abell, '32) inserted in the ears. Accentuated rouleau and clump formation could be seen in the venules and veins where the flow was slow. Such pseudo-agglutination did not appear to obstruct or interfere with the circulation. Erythrocytes passed from arterioles into the capillaries as separate cells.

The effect of injections of stilbestrol on adult male newts. A. Elizabeth ADAMS, Department of Zoology, Mount Holyoke College.

Stilbestrol¹ was administered intraperitoneally to adult male *Triturus viridescens* in doses of 0.5 mg. in 0.2 cc. of sesame oil once a week. Some animals were killed at the end of 3 weeks

¹ Stilbestrol supplied through the courtesy of Dr. C. W. Sondern, George A. Breon & Co., Inc., Kansas City, Missouri.

after the initial injection (total dose, 1.5 mg.); others, after a lapse of 2 additional weeks without injection (total dose, 1.5 mg.); still others, after treatment had been resumed, at 11 to 13½ weeks after the first injection (total doses: 4.5, 5.0, 5.5, and 6.0 mg.). Sesame-oil-injected and untreated newts served as controls.

At autopsy at 3 weeks, weights and structure of testes of stilbestrol-injected and of sesame-oil-injected newts were very similar; in both groups, mullerian ducts had enlarged somewhat. However, more prolonged stilbestrol-injections resulted in almost complete atrophy of testes, caused still greater hypertrophy of mullerian ducts and disturbed kidney structure. In controls, continued sesame-oil-treatment was associated with release of spermatozoa present at the start of the experiment followed by active spermatogenesis, especially spermiogenesis, and an average testicular weight of more than seventy times that of testes of stilbestrol-injected newts and more than three times that of untreated controls, whose testes still contained mainly spermatogonia, spermatozoa, evacuated cysts and some primary spermatocytes. No further hypertrophy of the mullerian ducts occurred in sesame-oil-injected newts although they remained larger than those of untreated controls and kidney structure appeared normal.

The arterial relations of the glomus caroticum in the rabbit. William H. F. ADDISON, Department of Anatomy, University of Pennsylvania.

The carotid body of the rabbit receives its arterial blood through a short vessel which originates from the carotid sinus close to the bifurcation of the common carotid artery. Serial sections stained for elastic tissue show that as the common-carotid artery approaches the bifurcation there is an increase of elastic tissue in the wall of one side of the artery. The elastic tissue increases and the smooth muscle diminishes and this half of the artery continues into the carotid sinus at the bifurcation. The other half of the artery remains more muscular in character and continues into the external carotid artery. Thus the carotid sinus differs in its structural details from the external carotid artery. The carotid sinus is thin-walled and its middle coat is mostly elastic tissue while the middle coat of the external carotid artery has much muscle in addition to elastic and other tissues. From the thin-walled elastic carotid sinus comes off the small artery to the carotid body. This artery has an elastic-tissue wall similar to that of the carotid sinus and divides at once to supply the carotid body. The carotid body forms a compact mass closely applied to the wall of the carotid sinus. Beyond the carotid sinus the media of the internal common artery changes and becomes chiefly muscular in its structure.

The sensory plexus on the visceral blood vessels of the rat. William F. ALEXANDER, Department of Microanatomy, Saint Louis University.

Microscopic preparations of the pelvic viscera of normal animals stained by the activated protargol technic, reveal a coarse, irregular nerve plexus surrounding the blood vessels in the inner zone of the adventitia. This plexus is particularly abundant in the walls of the smaller arteries and less profuse in those of the arterioles, veins and venules.

Degeneration of all the afferent and the preganglionic fibers, following destruction of the spinal cord and the spinal ganglia from the fifth or sixth thoracic segment caudalward, resulted in complete elimination of the plexus in the adventitia. The only fibers remaining in the vessels are the autonomic postganglionic fibers which innervate the smooth muscle of the media.

The coarse plexus in the adventitia obviously consists of afferent nerve fibers. By virtue of its location and the arrangement of its component fibers, it appears to be well adapted to be stimulated by caliber changes in the vessels.

Age-changes in the spleen of Wistar Institute rats and of man. Warren ANDREW, Department of Anatomy, Southwestern Medical College.

A study has been made of the spleens from 100 Wistar Institute rats and of 42 human beings. The rats ranged in age from 21 days to 1100 days and the human beings from newborn

to 92 years. Certain definite qualitative differences occur in the rat spleens at different ages. The youngest animals show only the beginning formation of Malpighian follicles, which appear as well developed for the first time at 50 days of age in our material. Germinal centers are present until the age of 550 days, after which they rapidly grow less conspicuous and are not seen in animals over 700 days old. In many of the senile animals the white pulp not only is small in amount but the Malpighian follicles are lacking so that the entire architecture of the spleen appears changed.

In animals which show germinal centers well developed, phagocytosis is an almost constant phenomenon in these locations. Degenerate lymphocytes break down and are ingested by macrophages. In senile animals whole lymphocytes may be ingested by macrophages free in the red pulp. While in younger animals the red pulp is primarily reticular in nature, in senile animals the sinusoids occupy a great deal of its volume.

Many similarities and some differences, chiefly of degree, are found in the comparison of age changes in the rat and in man.

A comparison of the spleen of Wistar Institute rats and of man at various ages. Warren AN-DREW, Department of Anatomy, Southwestern Medical College. Demonstration.

Slides and photomicrographs are presented to demonstrate the definite qualitative differences between the spleens of young, middle-aged, and senile rats. Hematoxylin and eosin stains show the decrease in size of germinal centers in middle age, the decrease in amount of white pulp, and the complete disorganization of the Malpighian follicles in many cases in advanced age.

Malloy's aniline blue stain is used to show the accompanying changes in the connective tissue. Hematoxylin-eosin-azure stain is used to show a definite difference in cell content of the red pulp in older specimens, in which plasma cells and lymphocytes with pyenotic nuclei are more abundant. In such senile animals the sinusoids are far larger and more conspicuous than in the younger and middle-aged specimens.

Slides are presented which show a definite degeneration of lymphocytes in apparently normal animals. In younger rats this occurs chiefly in germinal centers while in senile specimens it is often seen in the red pulp.

Spleens of senile human beings show the decrease in white pulp, a fact already well known, the sinusoidal nature of the red pulp, and many of the cellular changes seen in the rat.

Sex differences in pubic hair distribution. William B. ATKINSON and Herbert ELFTMAN, Department of Anatomy, and C. W. DUPERTUIS, Constitution Clinic, College of Physicians and Surgeons, Columbia University.

Pubic hair distribution has been examined in photographs of 1060 men and 309 women. The classical division into "masculine" and "feminine" types is found to be unsatisfactory. An adequate classification recognizes four types, designated as horizontal, sagittal, acuminate and disperse. The acuminate, or "masculine", type is present in one-half of the men and one-tenth of the women. The horizontal, or "feminine", pattern is the definitive type for nine-tenths of the women. It is also the basic type for male adolescents, is characteristic of 38% of 18-year-old males, and persists in 17% of the adult males. The decrease in frequency of the horizontal pattern with age in males is associated with increase in general hirsutism and is accompanied by the development of a disperse pubic hair pattern.

The cytoarchitecture of the cerebral cortex in the chimpanzee. Percival BAILEY, Department of Neurology and Neurological Surgery and Gerhardt VON BONIN, Department of Anatomy, University of Illinois.

The cytoarchitectural study of the chimpanzee's cerebral cortex was based on serial sections through 14 hemispheres. Sections in the three main planes were used, but oblique sections, at a right angle to the sagittal plane and cutting much of the tortuous central sulcus and the simi-

larly tortuous sylvian fissure at approximately a right angle proved to be the most useful. Within the neocortex, but excepting the insular cortex, 35 areas were recognized. These areas can be homologized with those of the human cerebral cortex as described by von Economo and Koskinas.

The chimpanzee's cerebral cortex shows a slightly broader inner granular and a somewhat narrower inner main layer (lamina V + VI) than the human one. The average relative breadths of the six layers are given for the chimpanzee and in brackets for man. Layer I: 9.5% (7.4%); layer II: 7.3% (6.1%); layer III: 26.9% (30.3%); layer IV: 9.8% (8.3%); layer V: 20.8% (16.9%); layer VI: 25.7% (31.0%).

A subdivision of the primate neocortex into three types appears to be closer to reality than Economo's well-known scheme of five types. The terms "diffuse", "eutectic" and "koniocortex" are suggested. The diffuse type is the agranular cortex of other authors; the new name is proposed because it is feared that "agranular" carries the misconception of a lack of a fourth layer. By definition, however, this layer contains the outer stripe of Baillarger and therefore is present in the "agranular" cortex in spite of the fact that Nissl preparations fail to reveal its extent. The koniocortex is found in the primary sensory areas OC, TC and PB. All remaining areas show a well-developed laminar pattern, but are so similar to each other that further subdivisions, by exaggerating minor details, would only tend to obscure the more obvious differences between eutectic and diffuse or koniocortex.

Structural indications of reduced thyroid activity in states of renal insufficiency. Burton L. BAKER, Department of Anatomy, University of Michigan.

In view of the occasional hints in the literature that colloid goiter may accompany some diseases in which the parathyroids are hyperplastic, and since delayed ossification is characteristic of cretinism and accelerated excretion of calcium is present in hyperthyroidism, it appeared possible that some functional interrelationship between the thyroid and parathyroid glands might exist. It was, therefore, of interest to observe the structure of thyroids from rats in which ureteral ligation or bilateral nephrectomy had induced a state of hyperparathyroidism as shown by physiological investigations of others and anatomical studies of the parathyroids from these animals.

Bilateral nephrectomy or ureteral ligation was performed on adult rats and the animals sacrificed, on an average, 50 hours post-operatively. Including littermate controls, over 100 animals were studied. In the thyroids, there was an increase in colloid, the follicular epithelium was reduced in height 19% in the females. Following the operations, the Golgi apparatus generally was reduced in size and, in more cells, possessed a compact form. Preliminary studies indicate that there may be a small reduction in the number of mitochondria. Sex and type of operation did not modify the response of the thyroid, showing that renal tissue is not essential to induction of the changes described. Such evidence suggests a probable inhibition of thyroid activity under these conditions.

Is the copulation plug essential for the en massé transport of spermatozoa into the uterine cornua of the albino rat? Richard J. BLANDAU, Department of Anatomy, University of Rochester. (Introduced by Charles E. TOBIN.)

The vesicular and coagulating glands of 20 sexually mature male rats were carefully ligated and removed. These males were subsequently mated with 74 females in heat. Successful ejaculation was confirmed by the examination of the vaginal vaults for spermatozoa. Forty-nine of the 74 females were followed for impregnations. Embryos were found in only one of the females. The remaining 25 females were killed at intervals of 3 to 135 minutes after ejaculation and their reproductive tracts were carefully examined for the location of spermatozoa. In 18 of the 25 females a mass of sperm, free from any plug material, was found in the vagina and no spermatozoa were found in the cervical canals nor in the uterine cornua. In

three females copulation and ejaculation appeared to be normal but subsequent examination failed to reveal spermatozoa in any part of their reproductive tracts. In two females mated with the experimental males small copulation plugs and sperm masses were found adherent to the lateral vaginal walls but no spermatozoa were present in the cornua. In another two females small vaginal plugs were observed cupped about the lappets of the cervix and numerous spermatozoa were found in the uterine cornua.

The cyclic changes in the tonus of the cervix of the albino rat. Richard J. BLANDAU, Department of Anatomy, University of Rochester. (Introduced by Karl E. MASON.)

Forty mature female rats were continuously observed for two consecutive reproductive cycles. Twelve hours before the expected onset of the third cycle 0.3 ml. of a trypan blue solution was injected through each cervical canal. The vaginal vaults of the females were then examined at one-half hourly intervals to determine the time at which the cervix would be in a sufficiently high state of tonus to retain the dye in the uterine cornua. The average length of time before the onset of heat that the cervix is sufficiently contracted to retain the dye injected into the cornua was 4.28 hours (range 1 to 8 hours). After its onset the high state of tonus is maintained for an average period of 8.5 hours (range 5 to 12 hours). Subsequent relaxation of the cervix begins, on the average, 4.03 hours (range 0 to 11 hours) before the end of heat. The average length of the entire period of cervical contraction was 12.8 hours (range 7 to 17 hours). The average length of heat for this group of females was 13.5 hours (range 7 to 21 hours). Dye injected into the uterine cornua at any time during the diestrus was not retained in the uterine cornua.

Pulmonary artery, a branch of the common carotid artery. Raymond F. BLOUNT and Edgar J. POTH, Departments of Anatomy and Surgery, University of Texas.

An individual is described in which the functional pulmonary artery is a branch of the left common carotid artery. This arises at the level of the cricoid cartilage and passes inferiorly, posterior and medial to the left internal jugular vein and then to the region of bifurcation of the trachea. Here it divides into right and left branches which pass to the lungs. At the point of bifurcation it is joined by a fibrous band representing the original pulmonary artery. This, and the aortic valves, show the condition of the heart not to be that of a truncus solitarius aorticus although there is but a single arterial trunk associated with an interventricular septal defect. There is a small patent foramen ovale. The aorta passes to the right. Its main branches are, in order: left common carotid, right common carotid, right subclavian and left subclavian. The left common carotid artery is of great size since it carries also the blood to the pulmonary artery. The left subclavian artery reaches the extremity by passing dorsal to the esophagus. The bronchial arteries are much enlarged. The right recurrent nerve loops about the right aorta but the left passes directly to its distribution. The thoracic duct joins the right innominate vein. There is a small left superior vena cava.

An embryological interpretation is offered for the aberrant vascular pattern.

Multinucleated neurons in Macaca mulatta. David BODIAN, Poliomyelitis Research Center, Department of Epidemiology, The Johns Hopkins University.

Multinucleated neurons are often seen in sympathetic ganglia but not elsewhere. Their abundance in brain-stem, spinal cord, and spinal ganglia of an adolescent rhesus monkey was therefore surprising. This strong, active animal was just recovering from an experimentally induced, mild attack of paralytic poliomyelitis when killed for histological study. Not only were many binucleated cells found in anterior horns, but there were also numerous cells with three nuclei, and some with four, five, and even six nuclei. The frequency of occurrence of multinucleated anterior horn cells was about 4% in the lumbar enlargement and about 1.5% in the cervical enlargement, estimated from 1180 15μ sections examined (ca. 15,000 cells).

Binucleated cells were also found in spinal ganglia, nucleus motorius tegmenti of the reticular formation, lateral reticular nuclei, inferior olives, cuneate nuclei, hypoglossal nuclei, and motor facial nuclei. No binucleated Betz cells or Purkinje cells were found. Multinucleated anterior horn cells varied from normal to more than twice normal size, but axon diameters were apparently normal. Some cells were of bizarre shape, and some vacuolated. Their nuclei varied from normal to $\frac{1}{2}$ normal diameter. Several nuclei could be seen packed into a small cell in some cases, or well-shaped in larger cells in others. Nuclei were normal in appearance except in cells which showed changes due to poliomyelitis.

The anatomy of intrahilar bronchiectomy. Edward A. BOYDEN, Department of Anatomy, University of Minnesota.

Seven plates are presented showing the arrangement of hilar structures ventral and dorsal to each lung and at the three fissures. The objective has been to provide an atlas of this region and to test to what extent the theory of broncho-pulmonary segments as surgical units of the lung may be realized anatomically. The terminology employed is that of Jackson and Huber (Dis. Chest, '43).

The dissections indicate that the arrangement of structures is such that individual ligation of vessels and bronchi is possible in 6 of the 18 broncho-pulmonary segments: namely, the two segments of the lingula, the two segments of the middle lobe and the superior segment of each inferior lobe. In the apical and basal regions, however, the venous drainage overlaps segments to such an extent (and individual branches are so difficult of access) that it is questionable whether the segments can be considered even as surgical units. For instance, the three segments of the right upper lobe are each drained by branches from both the ventral and dorsal divisions of the superior pulmonary vein, the latter is intersegmental in position and its segmental branches are too deep to be reached from the fissure. In the segments that are removable there are certain areas of double venous drainage. The left inferior bronchial artery may supply the right bronchus, etc.

Dissections of the auricular branch of the vagus in Macacus rhesus. S. R. BRUESCH, Division of Anatomy, University of Tennessee.

Eight dissections were made of the auricular branch of the vagus (nerve of Arnold) in 4 adult macaques. The nerve was followed from its origin to its termination by chipping away the petrous portion of the temporal bone.

All 8 dissections showed the same course and method of termination for the nerve: the auricular nerve travels through the petrous portion of the temporal bone from its entrance at the jugular foramen to the distal portion of the facial canal where it joins the facial nerve and appears to become incorporated into the facial sheath. The site of this junction is just proximal to the origin of the chorda tympani from the facial nerve.

These findings indicate that the gross relationships between the auricular branch of the vagus and the facial nerve in *Macacus rhesus* are substantially the same as those reported for the cat. Similar dissections on human material are being undertaken.

*Experimental discharge of neurosomes into spastic muscles of rats by thermal shock.*¹ Eben J. CAREY, Leo C. MASSOPUST, Walter ZEIT, Eugene HAUSHALTER, Department of Anatomy, Marquette University.

Morphologic evidence of the transmission of nervous substances or neurosomes, from motor end plates into spastic myoplasm was demonstrated. Neurosomes were ephemeral, pleomorphic, gold impregnated granules or bodies discharged from end plates. Neurosomes had variable affinity for lipoidal stains. Spastic paralysis was produced in 58 of 75 unanaesthetized rats

¹ Aided by a grant from the Baruch Committee on Physical Medicine.

immersed, except head and neck, one to ten seconds in water, 70°C. Spastic muscles excised different time intervals after immersion had abundant neurosomes during first four hours.

Neurosomes 10 to 500 microns long dispersed in myoplasm were first opaque, later their J and Q granules became aligned into cross striations. Ultraterminal branches of end plates were numerous. Some animals after 6 to 24 hours had flaccid paralysis, loss of end plates and abnormal striations. Junction of nerve and muscle was a protoplasmic continuum in different stages of flux. Abnormal motor impulses reflexly generated from thermal trauma applied to the skin were accompanied by exaggerated transfer of nervous material or neurosomes discharged from the superpermeable terminal axons of motor end plates and dispersed into the myoplasm of spastic muscle.

Studies on the inguinal region. II. The anatomy of the inguinal (Hesselbach) triangle. Simon B. CHANDLER, West Virginia University.

These observations on the inguinal triangle include studies on 268 body halves and the relation of twelve direct (diverticular) hernias to the parietal layers of the ventral abdominal wall.

Deep folds of the peritoneum may be produced by the urachus, the deep inferior epigastric arteries, and the obliterated hypogastric arteries. Plicae as tall as 4.1 cm. have been encountered. Some of the direct hernias occurred in these peritoneal fossae.

The aponeuroses of the internal oblique and the transversus muscles unite to form the conjoined aponeurosis. The inferior and medial extent of this aponeurosis varies considerably. The inguinal triangle varies widely as to the amount of muscular and aponeurotic tissue making up its wall. As a rule the muscular portion of the internal oblique extends further medially than the transversus.

If the conjoined aponeurosis is subjected to a bright light thinned out, fascial or even fatty areas are sometimes observed. Direct hernias have occurred in both the muscular and the aponeurotic portions of the triangle. If in the muscular part the muscle fascicles have been separated, hernias in the aponeurotic portion seem to occur in the weak fascial or fatty areas.

The strength of the inguinal triangle depends mainly on the presence or absence of fossae associated with the peritoneum, and the condition of the conjoined aponeurosis — is it muscular, fascial, or aponeurotic?

The pattern of upper femoral tributaries of the saphenous vein. Edward H. DASELER, Arthur F. REIMANN and Barry J. ANSON, Department of Anatomy, Northwestern University.

The saphenous terminations of the following tributaries were studied in 350 consecutive thighs: superficial pudendal, epigastric and iliac circumflex; medial and lateral accessory saphenous. The following arrangements occurred with the frequency indicated: all tributaries separately into the great saphenous vein, 15 per cent of cases; epigastric and iliac confluent, 15; iliac and lateral accessory confluent, 13; epigastric and pudendal confluent, 6; medial accessory saphenous and pudendal confluent, 8; epigastric, iliac and lateral accessory confluent, 33; epigastric and lateral accessory saphenous veins fused to terminate by common stem, 2; iliac and lateral accessory saphenous confluent, and pudendal and epigastric confluent to form lateral and medial common tributaries, 8 per cent.

Schemes occurred bilaterally in approximately 25 per cent of cases.

Role of the adrenal cortex in lymphoid tissue involution produced by inanition. Thomas F. DOUGHERTY and Abraham WHITE. Departments of Anatomy and Physiological Chemistry, Yale University.

Several histological and physiological alterations in lymphoid tissue are under pituitary-adrenal cortical control; most stimuli inciting involution of lymphoid tissue act via this hor-

monal mechanism. Inanition causes lymphoid tissue involution and also augments pituitary-adrenal cortical secretion. Experiments were conducted to ascertain whether lymphoid tissue involution during inanition was dependent on pituitary-adrenal cortical secretion.

Normal and adrenalectomized CBA strain mice, 8 to 10 weeks old, and weighing 20 grams, were fasted 48 hours. Inguinal, axillary, mesenteric lymph nodes, thymus and spleen were weighed in each animal. Adrenals were also weighed in unoperated mice. In the normal mice each lymphoid structure decreased approximately 50 per cent in total weight (as compared to fed mice) as a result of the fast. Adrenals in fasted mice were 30 per cent larger than in fed animals. In fasted adrenalectomized mice, no significant weight loss in lymphoid tissues occurred. Nitrogen analyses showed a 50 per cent loss of lymphoid tissue protein in normal, but no protein loss in adrenalectomized, fasted mice.

Lymphocytes are storehouses of proteins, the release of which is controlled by pituitary-adrenal cortical secretion. At least one of the proteins liberated from lymphocytes is identical with gamma globulin of serum. In inanition the pituitary-adrenal cortical mechanism is necessary for release of this reserve protein for metabolic purposes.

Elastic connective tissue in the ovary and uterus of the dog. Kenneth L. DUKE, Department of Anatomy, Duke University.

One ovary and a piece of uterus, from each of sixty-six dogs, were fixed in Bouin's fluid. The other ovary and a piece of uterus were fixed in Helly's fluid. Weigert's resorcin-fuchsin and Verhoeff's elastic stain were used to demonstrate elastic connective tissue.

The amount and distribution of elastic connective tissue in the ovary fluctuates during the reproductive cycle. In the prepubertal period the elastic tissue is confined to the blood vessels, particularly to the tunica intima. A similar distribution occurs in the ovary during the early stages of the first pregnancy and from proestrus to metestrus of the first infertile cycle. With the regression of the first corpora lutea there is an accompanying increase in elastic tissue. Many of the blood vessels in the medulla, especially veins and small arteries, develop a rather thick, laminated, elastic tunica externa. The connective tissue around the blood vessels and the capsules around the oldest corpora lutea become heavily infiltrated with elastic fibers. In the period between metestrus and the end of anestrus sprays of elastic fibers from the medulla extend into the superficial cortex; even the tunica albuginea may be infiltrated with such fibers.

Similar changes occur in the uterus. During the postestral phases and the postpartum period the elastic tissue of the blood vessels of both the myometrium and endometrium increases very markedly.

Response of nerves to repeated stretching. Donald DUNCAN, Department of Anatomy, Louisiana State University.

The sciatic nerves in three cats have been mobilized repeatedly and placed under mild tension by means of a silver pulley anchored to the muscles of the thigh. After eight operations on each nerve extending over a period of nine months the length of the nerves has been increased approximately 50%. In one cat that died of causes unrelated to the experiment, the peroneal division of the manipulated nerve measured 15 cm. between the proximal extremity of the great trochanter and the neck of the fibula, while the control nerve of the opposite side measured 10 cm. The nerves in the living cats are estimated to be lengthened by like amounts. Partial paralysis followed by recovery has occurred twice in each of the living animals and the third cat exhibited marked weakness of the triceps surae at the time of death. At no time has the force exerted been sufficient to abolish sensation. It is concluded that the sciatic nerve in the cat will increase greatly in length in response to long continued tension.

Some reproductive phenomena of the fur seal. Robert K. ENDERS, Oliver P. PEARSON, and Anita K. PEARSON, Edward Martin Biological Laboratory, Swarthmore College, and in cooperation with the Fish and Wildlife Service, U. S. Department of the Interior.

In the fur seal, *Callorhinus ursinus cynocephalus*, females approaching their first ovulation have large follicles in only one ovary, and the ovaries function alternately in parous adults. Only one follicle ruptures each year. Copulation occurs within a week after parturition and ovulation takes place when the involuting uterine horn has reached a dorso-ventral diameter of about 3 cm. Ovulation and implantation are both on the side that was not active in the previous year. Transuterine migration is unlikely because of the structure of the uterus. Gestation is approximately 1 year; the corpus luteum persists for more than a year. Blastocytes were found in the uterus or oviduct of four seals taken between July 10 and August 10. Since embryos have not been observed macroscopically in animals killed in November, and because the histology of the corpus luteum and blastocyst is similar to that of the marten and fisher, it is likely that there is a delayed implantation in the fur seal.

Torsion of the lower extremity. Herbert ELFTMAN, Department of Anatomy, College of Physicians and Surgeons, Columbia University.

The orientation of the neck of the femur and the axis of the talo-crural joint with respect to the knee joint is important in the functional activity of the lower extremity. Since the position of the neck of the femur cannot be accurately determined in the living, measurements were made on 35 male cadavers. The average outward rotation of the neck of the femur, or femoral torsion, was 11.9° , and that of a line bisecting the two malleoli was 27.4° . The large range of normal variation in both of these measurements is of practical importance. It is best indicated by the standard deviation, which was 6.2° for femoral torsion and 7.4° for malleolar torsion. Since the variations in orientation of the femoral neck and of the talo-crural joint prove to be independent of each other, combinations can arise which markedly affect the functional capacity of the lower extremity.

Regenerative processes induced by gonadotropic hormones in x-rayed ovaries of young Albino rats. J. M. ESSENBERG, Department of Anatomy, Chicago Medical School.

The rats selected were 30 to 40 days old. Fifteen were irradiated with 400 r and another 15 received two successive doses of 400 r. From each irradiated group 5 were separated, unilaterally castrated and reserved as controls. The remaining 20 rats were given subcutaneous injections of 10 to 15 R.U. of gonadophysin (G. D. Searle and Co.) every 4th day for 3 to 4 months and then autopsied. The injection started in different groups on the 1st, 2nd and 3rd week after irradiation. All injected rats were unilaterally castrated on the day of the first injection. Ten rats, littermates of the above, served as untreated controls.

Regenerative capacity of the ovaries varies with the dosage of x-rays, the concentration and length of injection period of gonadophysin and, to some extent, with the innate vitality of the animal.

The most uniform regeneration of the ovaries was obtained from the 400 r group. These were comparable to the untreated controls with the possible exception of greater follicular atrophy in the treated ovaries.

Greater variability in regeneration existed in the 800 r group. Most of the ovaries approached the condition of the 400 r rats while some resembled the ovaries of the x-rayed and uninjected controls. Large, well formed follicles were rare, atretic follicles were common. Small follicles were more numerous and showed less pathology. Corpora lutea were uncommon. Degenerating follicles resembled luteal tissue. Germinal epithelium was active in most ovaries and interstitial cells were abundant.

The x-rayed but uninjected controls resembled senile ovaries. Follicles, if encountered at all, were pathologic. Small follicles, on degeneration, resembled tissues of corpora lutea. Rarely was the germinal epithelium more than a layer of mesothelium. Interstitial cells were common.

Length reactions to moisture by human long bones (Egyptian provenience). Gertrude S. EVANS, Research laboratory, 350 South Main street, Freeport, New York. (Introduced by Thomas Horace EVANS.)

Human bones shorten if dried, lengthen if wet. Heinrich Werner (1897) gave 2.0 mm. difference. Later, Karl Pearson and Alice Lee found femoral variations of 2.6 mm. Ancient bones react also.

This paper studies length changes in different areas of femora of over 3,000 years antiquity (Egyptian provenience, courtesy Brooklyn Museum). Bones carefully cut with jewelry saw into unequal thirds. Parts weighed and measured, then covered with water. Weighed and measured on several dates. (Water discoloration appeared.) Finally, dried on glass plates, 24 hours at room temperature. Concluding weights and lengths taken. Percentage comparisons made. Measuring box used.

1. Weights increased, decreasing after drying, becoming less than at first instance (showing material change), except for head portion (with some shaft adjoining) of femur S-106-A, right. This remained plus 2.2 gm., (slight longitudinal splitting at shaft).

2. Lengths increased, except for medial condyle, femur S-61, left. Lengthening persisted (especially in portions of femur S-19, left). Others lengthened on earlier dates, shortening when dried.

3. Shaft parts increased more in proportionate lengths than end parts, although the latter absorbed more water. (Resistant supporting arcades, or slight changes in angle of neck may modify head piece measurements.)

Lipids in the corpora lutea of the cyclic rat. John W. EVERETT, Department of Anatomy, Duke University.

The Schultz modification of the Liebermann-Burchard reaction proves peculiarly useful in microscopic study of corpus luteum fats. Such reactions are indicative of unsaturated steroids (Fieser). Employing this test in company with other methods, the corpora lutea of normal cyclic rats have been reinvestigated, comparing them stage by stage with similar elements from rats of the DA strain.

The normal corpus luteum, as Dempsey and Bassett state, undergoes a substantial increase of lipid midway in diestrus, reaching a maximum during the subsequent estrus. Meanwhile, however, there intervenes in the last hours of diestrus and during proestrus a marked temporary reduction of sudanophile, birefringent and Schultz-positive material, a fact which these authors failed to mention. It is during this very period that other evidence suggests transitory progesterone secretion.

In distinct contrast, corpora lutea of DA rats during the latter half of diestrus, proestrus and estrus are largely negative in the Schultz test and contain few birefringent crystals. Replicas of normal corpora were regularly found, however, in DA persistent-estrous rats in which experimental cycles had been maintained by suitable lactogen therapy (Everett, '44). It is believed that cyclic DA corpora lutea in the absence of such treatment are truly inactive or nearly so, while those of normal rats are moderately activated. The positive Schultz test somehow reflects this activity.

Storage of lipids in corpora lutea of rats after artificial termination of pregnancy by estrogen injection. John W. EVERETT, Department of Anatomy, Duke University.

The Schultz test was applied to frozen sections of 10 pairs of ovaries from rats in the sixth to sixteenth days of gestation. The corpora lutea developed at best a barely perceptible pale

green tint and often no color whatever. Rarely, an isolated cell was colored a distinct blue-green characteristic of unsaturated steroid substances.

Studies of cyclic corpora lutea had indicated that accumulation of Schultz-positive lipids is in some manner a result of luteotropic stimulation. Since deposition of these reactive substances occurs most markedly after the onset of a new estrus, 50 μ g. of estradiol benzoate was administered to each of 7 rats which were 4 to 17 days pregnant. Two days later, following removal and examination of the ovaries, nearly every parenchymal cell in the pregnancy corpora lutea contained an abundance of sudanophile, Schultz-positive material, much of it in the form of birefringent crystals. No variation in lipid content was recognized which with certainty could be correlated with gestation chronology. Pregnancy was probably interrupted in each instance, for new corpora were usually identified and resorption of embryos was in progress in the more advanced cases.

Preliminary study indicates a similar effect of estrogen on luteal tissue in the absence of the hypophysis, provided that the corpora lutea are maintained by daily lactogen injections.

Studies on the effectiveness of adrenal cortex extract and desoxycorticosterone acetate in adrenalectomized rats fed diets free of proteins or carbohydrates. Wilburn J. EVERSOLE, Department of Biology, The Rice Institute.

Male rats, after weaning, were fed a stock diet until they had reached a weight of 50–60 grams. The animals were then adrenalectomized, fed synthetic diets (Eversole, '45) free of proteins or carbohydrates and given daily, either 0.5 cc. of adrenal cortex extract or 0.2 mg. of desoxycorticosterone.

Eleven of twelve adrenalectomized rats, injected once daily with desoxycorticosterone and fed a protein-free diet, survived for 10 days, but none of the rats lived beyond the nineteenth day of treatment. The weight loss for the first 10 days averaged 0.5 gm./day, and this loss was comparable to that observed in intact controls on the same diet.

Desoxycorticosterone injected daily was ineffective on growth and survival in adrenalectomized rats fed a carbohydrate-free diet, but adrenal cortex extract administered in the drinking water was highly beneficial and all animals survived as long as treatment was given (20 days for one group). However, one injection per day of cortical extract was seemingly of little, if any, benefit.

*The effect of menopause on the voluntary running activity in the albino rat.*¹ Edmond J. FAR-
RIS, The Wistar Institute of Anatomy and Biology.

The voluntary running activity of two series of albino rats was followed during their entire life span. Series I, consisting of seven rats, was maintained under normal colony conditions; and series II, consisting of eighteen rats, in reversed 12-hour light-dark schedule.

The females exhibited regular 4-day bursts of activity associated with estrus during the normal adult life. With advancing age there was a marked change in the character of the activity. Series I showed a disturbance in the regularity of the activity cycle beginning on average day 345 (range 221 through 550); series II at 371 days (range 253 through 658 days). During the menopause there were unusually high peaks of running activity.

A new activity rhythm was evident during post-menopause, which began in rats of series I at average age of 454 days; while in series II the average age was 502 days. Relatively regular activity bursts occurred in series I at 18-day intervals, and in series II at 17-day intervals. There was a general lowering in the amount of voluntary running with the increase in age until death.

It is concluded female rats exhibit irregular increased bursts of activity during menopause. The post-menopause is characterized by rather regular bursts of voluntary running at 17- or 18-day intervals.

¹ Aided by a grant from The Samuel S. Fels Fund.

Succinoxidase and succinic dehydrogenase in the developing cerebral cortex of the fetal pig.

Louis B. FLEXNER and Josefa B. FLEXNER, Department of Embryology, Carnegie Institution of Washington, and the Poliomyelitis Research Center, Department of Epidemiology, The Johns Hopkins University.

These studies are a continuation of earlier ones in which an effort was made to correlate histological changes in the developing cerebral cortex of the fetal pig with changes in activity of respiratory enzymes.¹ Succinic dehydrogenase was measured by three methods with essentially parallel results: the dehydrogenase activity is low up to a gestation age of 60-64 days; then triples in activity to term when it is approximately equivalent to that found in adult cortex. This critical period from 60-64 days corresponds to that found for increase in cytochrome activity and is also one of the two critical periods noted in the histogenesis of the cerebral cortex.

Succinoxidase activity depends upon the activities of succinic dehydrogenase, cytochrome and cytochrome oxidase. Its determination should serve as a check in the earlier determination of cytochrome which permits the prediction that succinoxidase activity will be at about zero level during the first 60 days of gestation and then increase. The experimental findings substantiate this prediction. At birth, succinoxidase activity is about equivalent to that of the adult cortex.

¹ Flexner, J. B., L. B. Flexner and W. L. Straus, Jr. 1941 J. Cell. and Comp. Physiol., 18, 355.

The motor and sensory axons of the great splanchnic nerves with special reference to the decussation of motor fibers James O. FOLEY, University of Alabama.

The motor fibers were removed from the great splanchnic nerves of three cats by cutting the roots of the first nine thoracic spinal nerves. In two other cats the motor and sensory fibers were deleted by removing the dorsal root ganglia of the first nine thoracic nerves.

Histological examination of sections of the silvered nerves of these two types of preparations showed: (1) that most of the axons in the great splanchnic nerves are sensory and (2) that occasionally the motor fibers decussate across the vertebral column to enter the great splanchnic nerve of the opposite side.

These observations do not support the belief that the splanchnics are composed largely of motor fibers from the white rami and it can no longer be assumed that the motor fibers are ipsilateral in all cases.

A Marchi study of the distribution of the anterior commissure in the monkey. Clement A. FOX and Walter RAMBACH, Institute of Neurology, Northwestern University and Department of Anatomy, Marquette University.

With the Horsley-Clarke stereotaxic instrument lesions were placed directly in the anterior commissure of three monkeys, destroying the fibers of this system as they cross the midplane of the cerebrum. Three weeks later these animals were killed. Subsequent staining by the Swank and Davenport modification of the Marchi method failed to show an anterior limb of the commissure. The large degenerated posterior limb of the commissure could be followed into the inferior end of the external capsule in which it passed posteriorly. In this course its fibers gradually diminished and disappeared at the level of the hippocampus. Some of these fibers entered the medullary center of the middle temporal gyrus.

In two Weil stained normal monkey brains used to supplement this study it was not possible to identify an anterior limb of the commissure by differential staining as can be done in similarly stained normal cat brains. In the cat the anterior limb is more heavily medullated than the posterior limb and stands out in sharp contrast. It would seem that if an anterior limb is present in the monkey it must have the same medullation as the posterior limb; that proportionately it is a much smaller component than it is in the cat; and that the majority of the fibers of the commissure in the monkey belong to the posterior component.

Influence of estrogens upon the bones of young and old mice and of thyroid deficient mice.

W. U. GARDNER and D. H. CLOUET, Department of Anatomy, Yale University.

Mice that receive estrogens, beginning at the time of weaning or early in life develop an increased amount of intramedullary bone. The breaking strength, amount of ash, and density of the bones increase. In the present studies old (267 to 378 days) and young (37 to 47 days) hybrid mice were given subcutaneously six weekly injections of 25 μ g. estradiol benzoate and were killed 37 and 38 days after the first injection. Untreated littermates served as controls. Purina fox chow and water were fed. During the period of treatment the testicular weights were unaltered although seminal vesicles and prostates were small in the estrogen-treated mice. Body weights were not changed. The weights of the dry femurs, the ash, and calcium content of the femurs of the old estrogen-treated mice were slightly greater than the controls—ash weights were 35.99 and 32.78 mg. or 101.09 and 99.81 mg. per 100 gm. body weight for the two groups respectively. Among the young group the femurs of the estrogen-treated mice contained 29.91 mg. ash and the controls 24.05 mg., a significant increase, or 117.22 and 93.58 mg. per 100 gm. body weight respectively. Estrogen-treated and control young mice, made hypothyroid by feeding 2 per cent thiourea with their food, showed comparable osseous differences, 24.47 and 17.35 mg. ash per femur, respectively or 118.8 and 85.47 mg. per 100 gm. body weight respectively. The smaller weights of ash in this group were due to failure to increase in body weight on the thiourea diet. Radiographs and histological sections also revealed increased density and an increased number of osseous spicules in the femurs of the estrogen-treated mice paralleling the ash and calcium content.

*The efferent fibers of the parietal lobe of the cat (*Felis domesticus*). Walter G. GOBBEL, Jr. and George W. LILES. Department of Anatomy, Duke University. (Introduced by Talmage L. PEELE.)*

The left parietal lobes of fourteen adult cats were exposed and ablations of the cortex were done using Garol's map of the sensory cortex as a guide for the limits of the excisions. Complete anatomical studies were done upon six of these animals using Busch's modification of the of the Marchi method for the myelinated fibers and gallocyenin for studies of cytoarchitecture.

The cortical pattern was found to be composed of six layers which were similar throughout the parietal lobe save for an increase of depth of the molecular layer posteriorly. No Betz cells characteristic of the motor cortex were seen.

The parietal lobe was found to send association fibers to adjacent homolateral cerebral lobes and commissural fibers by way of the corpus callosum to the contralateral parietal lobe. Parietothalamic fibers terminated in the nuclei ventralis posterolateralis, ventralis posteromedialis, posterior and pulvinar. Parieto-tectal fibers ended in the superior colliculus. Parieto-spinal fibers were found to accompany the pyramids to the spinal cord in which they were associated with the lateral cortico-spinal spinal tracts of the opposite side where they rapidly ran out in the cervical region.

The functional significance of this parietal projection system was reviewed and from this investigation it was felt that the most plausible function was one of a sensitization mechanism for sensory neurones.

The union of the nasal septum with the palate in the dog. Melvin C. GODWIN, Department of Anatomy, University of South Dakota.

After the palatine processes join in the midline a sheet of epithelial cells buried in the connective tissue marks the line of fusion. A thickening of the epithelium forms on the cephalic surface along the line of union. On each side of the thickening the epithelium loses its union with the connective tissue for a distance of over half of the width of the palatine process. The epithelium of the nasal septum unites with the palate epithelium ventrally. The thickened epithelium along the midline of the palate becomes free and retracts ahead of the advancing

nasal septum. The epithelium on the nasal septum is progressively stripped from its connective tissue in a ventrodorsal direction. The epithelium of the palate lateral to the thickening along the midline is already free and is raised up by the pressure of tissue fluid which collects under it. As a result the connective tissue of the nasal septum and the palate are brought into apposition progressively dorsally without interference by epithelium. The force which strips back the epithelium is apparently the pressure in the "blisters" on each side of the midline.

*An experimental study of acute inflammation in the nervous system.*¹ Robert A. GOOD and Berry CAMPBELL, Department of Anatomy, University of Minnesota.

The hematogenous origin of the acute inflammatory cells shown by Maximow and Kolouch in connective tissue has been demonstrated in the central nervous system. Kolouch's method of hour-by-hour examination following injection of eggwhite into the tissues was adapted to the problem and a series of micro-injections into the cerebral cortex and spinal cord of rabbits has been studied at from 1- to 24-hour stages. In addition to sections, Romanowsky-stained smears and imprints were studied after the method of Dougherty. A stasis of blood in the capillaries near the lesion, with exfiltration of neutrophils and lymphocytes, occurs before 2 hours. The former cells, while active in all early stages, take no part in the formation of the cuff or of macrophages. A cycle of changes leads the lymphocytes through the polyblast stage to forming active macrophages. The great preponderance of hematogenous cells around the lesion obscures the participation of resident glial cells in this cycle. Other methods are being applied to the study of glial changes.

¹ Aided by a grant from the National Foundation for Infantile Paralysis.

Influence of hormones and cobalt on the anemia induced by hemorrhage in the thyroidectomized rat. Albert S. GORDON, Patricia C. KADOW and Harry A. CHARIPPER, Department of Biology, Washington Square College, New York University.

Total red and white cell, hemoglobin and reticulocyte responses were studied in 73 thyroidectomized and 37 normal adult male rats subjected to a single large bleeding (4-6 cc.) and given various treatments following the blood withdrawal. Removal of the thyroid inhibited both red blood cell and hemoglobin regeneration. Daily injections of 0.1 mg. thyroxine accelerated recovery from the hemorrhagic anemia. Injections of 0.5-1.25 mg. testosterone propionate were without significant influence on the course of the anemia in thyroidectomized animals; the combination of 1.25 mg. testosterone propionate and 0.1 mg. thyroxine daily, however, proved to be a slightly more effective treatment than thyroxine alone. Even more pronounced increases in the numbers of red cell were obtained in bled thyroidectomized rats given daily injections of 1.25 mg. cobaltous nitrate. The greatest increases in red cells and hemoglobin were seen in thyroidectomized animals subjected to the joint treatment of cobaltous nitrate (1.25 mg. daily) and thyroxine (0.1 mg. daily). Although the height of the reticulocyte peak due to the bleeding was not altered by any of the treatments, higher reticulocyte values were maintained throughout the experimental period in those animals receiving thyroxine, testosterone and cobalt, singly or in combination. Total white cell counts showed considerable fluctuation and appeared to be unaffected by any of the experimental treatments.

The termination and attachment of muscle fibers within human muscles. Charles M. GOSS, Department of Anatomy, University of Alabama.

Dissection of well preserved human muscles revealed that the fibers have a definite arrangement within fasciculi. Material was obtained from dissecting room cadavers embalmed with formalin, phenol, alcohol, and glycerine. Separation of individual fibers was made by dissection under a stereoscopic microscope. No chemical treatment or maceration was employed. Both muscle and connective tissue elements were studied.

Arrangement of fibers is dependent on length of fasciculi. Average length of fibers is 10 cm. if length of fasciculi permits. In fasciculi of less than 10 cm. practically all fibers extend the full length, attaching to tendon at both ends. In fasciculi of 10 to 20 cm. the great majority of fibers have one end attached to tendon and one end terminating within the bundle. In fasciculi of more than 20 cm. fibers may have both ends within the bundle.

Terminations within fasciculi are either long gradually tapering points or are blunt like those at tendons. Most pointed ends are attached to adjacent fibers of full diameter by an intermingling of the argyrophilic fibrillae of the sheaths of the two fibers. The argyrophilic sheaths of blunt endings become minute tendons approximately 50 micra long which attach to other fibers, producing the smallest possible two bellied muscles. Many tapering points also attach to intermediate tendons. The longest fiber so far encountered was 14 cm. from a human sartorius fasciculus 38 cm. long.

A cortico-bulbo-reticular pathway from area 4-S. W. S. McCULLOCH, C. GRAF, and H. W. MAGOUN, Department of Psychiatry, University of Illinois and Department of Anatomy, Northwestern University.

Previous work by one of us and associates has shown that the arrest of cortical electrical activity evoked from the supressor areas of the cortex involves a recurrent circuit through the basal ganglia. These structures were not found essential, however, for the suppression of cortical motor response evoked from area 4-S. The demonstration of a bulbar mechanism inhibiting motor activity (see Magoun and Rhines) made it of interest to determine whether the supressor or other portions of the cortex were related to it.

Areas of the cortex were activated with strychnine and records of the electrical activity within the lower brain stem were observed for potential changes related to cortical spiking. Alterations recorded from the pyramid on activating area 4 provided a type for comparison with other data.

Similar potential changes on recording from the medial portion of the bulbar reticular formation were evident upon activating area 4-S, and were possibly present upon activating area 2-S. They were not prevented by section of the pyramid at the caudal margin of the pons. No related electrical alterations were observed in the bulbar reticular formation upon activating other cortical areas.

These results indicate the presence of a direct connection from area 4-S to the bulbar reticular formation and contribute to our understanding of the organization of an important component of the extra-pyramidal motor system.

A quantitative study of some components of the testis. D. J. GRAY, Department of Anatomy, Stanford University.

An entire para-sagittal section from the left testis of a subject 43 years of age was subjected to measurements by means of a planimeter and the areas occupied by various components were determined. The total area of this section, which contains none of the mediastinum testis, is 0.75 square inches. The tunica albuginea occupies 15.37% of this area. The seminiferous tubules, including their basement membranes and tunicae propriae, comprise 42.28%; of these tubules the epithelial portions along with their cavities make up 21.19%. The interstitial tissues include 42.34% of the section.

A similarly-located section from the left testis of a subject 69 years of age has a total area of 0.72 square inches. The percentages of the total area occupied by various components are as follows: tunica albuginea, 10.86%; seminiferous tubules, including basement membranes and tunicae propriae, 46.57%; the epithelial portions of these tubules together with their cavities, 31.06%; and the interstitial tissues, 41.91%. Six-tenths per cent of this section is comprised of fibrosed tubules.

A statistical analysis of the measurements of the seminiferous tubules indicates a significant difference between the areas of the tubular sections of one testis and those of the other; on this basis the probability that the two sections were taken from similar testes is less than 1 in 1,000,000.

The Nissl substance of the ciliary ganglion cells in the chicken. Mary E. GRAY, Department of Anatomy, Vanderbilt University.

The ciliary ganglion of the chicken is divided into two zones: a proximal containing large cells with synaptic endings in the form of calyx, brush and arborescent types; and a distal containing small cells surrounded by pericellular plexuses. In the proximal zone most of the cells contain coarse flakes of Nissl material which tend to concentrate around the nucleus. Toward the periphery the concentration gradually becomes less marked and the peripheral zone is relatively free of granules. Variations from this pattern occur. Some cells have a sharply defined perinuclear ring of Nissl substance, the material being so condensed that individual granules cannot be seen. A few cells have their cytoplasm filled evenly with large flaky Nissl granules. A rare type contains small Nissl granules scattered evenly throughout the cytoplasm, with the addition of a peripheral cap of larger, densely packed granules over that end of the cell containing the nucleus.

In the region of small cells classification of the Nissl patterns is difficult, due to the relatively scant cytoplasm. Individual granules are large, but in some cells they are concentrated in a ring against the nuclear membrane, while in others they are concentrated at the periphery, leaving a zone of clear cytoplasm about the nucleus.

These cells resemble those of the chicken's superior cervical sympathetic ganglion more closely than those of the dorsal root ganglia.

*Blood supply of the cat's spinal cord.*¹ Richard A. GROAT, Institute of Neurology, Northwestern University.

Specimens were prepared by perfusing through the heart first with a gum acacia, sodium chloride water solution, then with a gum acacia sodium chloride formalin solution, then with gum acacia, sodium chloride water solution again to flush formalin from the vessels, and finally with a gelatin, India ink, sodium chloride water solution.

The ventral longitudinal artery is a series of elongated anastomotic loops. The two dorsal longitudinal arteries are single channels located between the cord and the dorsal roots. They receive their most rostral contributions from the vertebral arteries on the medulla, and course the length of the cord. Radicular arteries lie on the ventral side of most ventral roots. Each usually branches just peripheral or just central to the radicular line of dural reflection. A ventral branch continues medially amidst or close to the ventral rootlets and joins the ventral longitudinal artery. A dorsal branch passes dorsally on the cord and joins the homolateral dorsal longitudinal artery either under cover of the dorsal rootlets or in the open between series of dorsal rootlets. There are no vessels which properly could be called dorsal radicular arteries.

More veins are associated with ventral than with dorsal roots. All empty into the homolateral ventral longitudinal vertebral sinus, which is drained segmentally. These sinuses also communicate copiously with the basi-vertebral sinuses.

¹ Work done under contract with the Office of Scientific Research and Development. Permission to publish this paper has been granted by the Committee on Medical Research, A. N. Richards, Chairman.

The acinar content of thyroid glands from patients treated with thiouracil. Béla HALPERT and Joseph M. THURINGER, Department of Pathology and Department of Histology and Embryology, University of Oklahoma.

The acinar contents of thyroid glands from patients with hyperthyroidism were studied. Formalin-fixed tissues were stained with H and E., Haidenhain's azocarmine, and by van Gieson's method. In two patients who received thiouracil only preoperatively, occasional medium-sized acini contained thin finely granular colloid, few scattered acini contained ir-

regular central masses of dense colloid staining bright red with azocarmine. These masses had a pale blue halo. Most of the remaining acini were partly filled with thin pale to almost colorless reticulated colloid or were empty. In three patients, subtotal thyroidectomy was performed in two stages. In preparation for the first stage Lugol's solution only was given. In preparation for the second stage thiouracil was given. Thus, the effects of iodine and thiouracil could be compared and contrasted in the same patient. Following Lugol's solution alone, acinar colloid was dense. Following thiouracil, although remains of dense colloid could be seen in many acini others presented a pale reticulated colloid or were empty. The appearance was similar to that following thiouracil alone. In two patients who received iodine following treatment with thiouracil, some acini were empty, others contained thin light or dark blue stained colloid. According to these observations acinar colloid diminishes in quantity and density or disappears under the influence of thiouracil.

Interrelation of pituitary gland and testes during initial stages of sexual maturation in humans, as indicated in studies of three boys during early adolescence. James B. HAMILTON, Department of Anatomy, Long Island College of Medicine.

Studies were made of 3 boys upon their castration during early adolescence when they were, respectively, 13-3/12, 14-4/12, and 15-5/12 years of age and were in stages 3, 3, and 3-4 of the scale of sexual maturation described by Greulich and associates. Before orchietomy titers of urinary gonadotrophins were in all cases less than 3.5 M.U. per 24 hours. After castration the values in case 1 were 120 M.U. at 3 weeks and 80 M.U. at 6 weeks; in case 2, 50 M.U. at 4 weeks, 120 M.U. at 13 months and 100 M.U. at 18 months; in case 3, 30 M.U. at 3 weeks and 40 M.U. at 6 weeks. Apparently then, the pituitary gland is capable of considerable secretory function in early adolescence but this potential function is greatly limited by the presence of the testes. Dorman's studies show that the quantity of androgens present at this stage (again as judged from urinary titers) is only a small fraction of that present in adults. Daily intramuscular injection of case 1 with 10 mg. of testosterone propionate for 30 days reduced the daily values for urinary gonadotrophins from a supranormal, castrate level of 80-120 M.U. to < 3.5-7 M.U. This dosage of androgen has been shown previously (Catchpole, Hamilton, Hubert) to be insufficient to so markedly lower the values for urinary gonadotrophins in the adult eunuch.

Volumes of caudate-putamen complex in primates. Pinckney J. HARMAN, Georgetown University Brain Research Institute.

A previous preliminary study of the volumes of certain of the basal ganglia has indicated that the emergence of the putamen as the predominant nucleus of the caudate-putamen complex is a prominent feature in primate development.

This has been tested by estimations of the volume of these constituent nuclei in the lemuroid Galago, the monkey Macaca, the anthropoid Pan, and in man. A comparison of the absolute magnitudes of these volumes may be obtained by dividing the value for caudate into the value for putamen. The resultant ratios are as follows: Galago demidovii 0.65, Macaca mulatta 1.3, Pan satyrus 1.7, Homo sapiens 1.8. An attempt at evaluation of the relative significance of morphological and functional affinities with respect to those changes is in progress.

The termination of the tail of the caudate nucleus in primates. Pinckney J. HARMAN, Georgetown University Brain Research Institute.

The termination of the tail of the caudate nucleus has been studied in cell and fiber preparations of two lemuroids, Galago demidovii and Perodicticus potto; three monkeys, Macaca mulatta, Cercopithecus aethiops sabaues and Cebus fatuellus; and man.

Galago — The ventral limbs of the caudate expands into a massive enlargement (Colliculus terminalis) which lies dorsal to the amygdala. Followed rostrally this enlargement rapidly

disappears in the region of the dorsolateral angle of the caudal pole of the putamen. Thus, in Galago there is no apparent fusion of the caudate tail with any other nucleus.

Potto — The ventral limb also expands, but to a lesser degree than in Galago, and comes to lie ventral to the caudal pole of the putamen with which it fuses at the level of the caudal pole of the amygdala. At this level the tail lies dorsal to the amygdala from which it may be distinguished histologically.

Monkeys and man — As the tail assumes its relation to the inferior horn of the lateral ventricle it expands, and comes to lie ventral to the putamen. In its rostral course it grooves the dorsolateral aspect of the amygdala; however, it remains distinct from this complex and passes forward to end by fusing with a ventral process of the putamen.

Intramedullary potentials following stimulation of the cervical vagus. Frank HARRISON and S. R. BRUESCH, Division of Anatomy, University of Tennessee.

Potentials were recorded with a cathode ray oscillograph from the medullae of forty-six cats following stimulation of the cervical vagus. Nembutal or urethane anesthesia, or decerebration were used. Recording electrodes were oriented with a Horsley-Clarke instrument.

The following potentials were recorded best near the level of the obex: (1) $1\frac{1}{2}$ to 3 msec., (2) 4 to 5 msec., (3) 7 to 11 msec., (4) 12 to 20 msec., and (5) 20 to 45 msec. following the stimulus.

The fastest waves were recorded farthest laterally on the ipsilateral side near the entrance of the vagal rootlets. The slowest waves were found in the reticular formation near the midline just dorsal to the inferior olivary complex. These waves were best ipsilaterally but were obtained also contralaterally. The intermediate waves were found in an area extending 4 mm. ipsilaterally to as much as 2 mm. contralaterally, from 2 mm. caudal to the obex to 4 mm. rostral to it, and in depth from the inferior olivary nuclei to 4 mm. dorsal to those nuclei.

This area coincides with the region outlined by Magoun and his co-workers as the respiratory centers.

Muscular associations of the oblique cord. J. C. HAYNER, William Waldo Blackman Laboratory of Anatomy, New York Medical College. (Introduced by James W. BENJAMIN.)

The left oblique cord (chorda obliqua) in eight cadavers was found distinct from all muscular tendinous fibers in only one case. In seven cases fibers were prolonged from its distal extremity into muscular elements of the flexor pollicis longus. In two cases some fibers of flexor digitorum profundus arose from the proximal extremity. In one of these two cases a centralis muscle arose from the middle of the oblique cord and two tendinous slips from the biceps brachii were inserted into the oblique cord.

Notes on the inguinal region. J. C. HAYNER, William Waldo Blackman Laboratory of Anatomy, New York Medical College. (Introduced by James W. BENJAMIN.)

In the area of the lunette in Hesselbach's triangle the so-called transversalis fascia is fundamentally derived from true transversalis fascia, transversus muscle, intermediate fascia, internal oblique (cremasteric) muscle and superficial internal oblique (cremasteric) fascia, but maldevelopment, absorption and fusion may reduce stratification and muscular or fascial elements in a variable manner. The so-called transversalis fascia of the femoral sheath at times consists of two layers—derivatives of the internal oblique and transversus muscles. The internal oblique and transversus muscles decussate with each other in forming the cremasteric tunic of the cord at the abdominal inguinal ring, and the intermediate fascia becomes lost in that tunic. The abdominal inguinal ring should be regarded as a passage formed by transversalis fascia, transversus muscle, intermediate fascia and a deep lamella of the internal oblique muscle. Those same muscular elements form the aponeurotic portion

of the inguinal falx, concealed by the more nearly vertical fasciculi of the superficial lamella of internal oblique muscle and by its superficial fascia, and superposed upon the transversalis fascia, which fuses with the aponeurosis at the linea semilunaris.

On a normal human ovum not over 7½ days of age. Arthur T. HERTIG and John ROCK, Free Hospital for Women, Brookline, Mass., Departments of Pathology, Obstetrics and Gynecology, Harvard Medical School and Department of Embryology, Carnegie Institution of Washington.

The ovum (Carnegie 8225) was discovered, after partial fixation, in a bicornuate uterus removed surgically on the twenty-second day of the cycle. Its implantation site was anterior, fundal, without vascular reaction, and just to the left of the midline (corpus luteum left). It appeared as a slightly raised but flattened, bowl-like object measuring 0.39 mm. in diameter, covered by a glistening membrane which partially concealed the eccentrically-situated 0.07 mm. embryonic mass.

Microscopically, the endometrium is in the twenty-first day of its cycle with marked stromal edema and active glandular secretion. The chorion measures $0.120 \times 0.306 \times 0.330$ mm.; the chorionic cavity $0.030 \times 0.200 \times 0.228$ mm.; the embryo $0.036 \times 0.078 \times 0.090$ mm. and the amniotic cavity $0.006 \times 0.054 \times 0.060$ mm.

The ovum, a two-thirds implanted blastocyst, possesses trophoblast similar to Carnegie 8020 and varies from a thin indifferent blastocyst wall (abembryonic pole) to a thick shell of primitive syncytio- and cytotrophoblast (embryonic pole). Active invasion and phagocytosis of maternal stroma by syncytiotrophoblast is a prominent feature.

The chorionic cavity is distorted and crowded by an eccentrically-placed, bilaminar germ disk. The amniotic cavity is merely an irregular slit between ectoderm and amnion, the latter arising from trophoblast. Mesoblasts, also apparently arising from trophoblast, are present at the embryonic pole but the exocoelomic membrane (Heuser's) has not appeared.

On a normal ovum of approximately 9 to 10 days of age. Arthur T. HERTIG and John ROCK, Free Hospital for Women, Brookline, Mass., Departments of Pathology, Obstetrics and Gynecology, Harvard Medical School, and Department of Embryology, Carnegie Institution of Washington.

The ovum (Carnegie 8215) was discovered in a uterus removed surgically on the fifty-sixth day of the menstrual cycle (periodicity infrequent and irregular). Endometrial histology indicated a typical twenty-fourth day secretory phase with ovulation having occurred approximately 10 days before.

The implantation site was posterior, at the cornu opposite the ovary of origin, and without visible vascular response. It appeared as a slight elevated area measuring 0.57 mm. in diameter surmounted by a tiny 0.115×0.154 mm. area of ulceration.

The chorion measures $0.207 \times 0.498 \times 0.525$ mm.; the chorionic cavity $0.100 \times 0.210 \times 0.228$ mm.; the embryo $0.050 \times 0.052 \times 0.084$ mm. and the amniotic cavity $0.022 \times 0.048 \times 0.050$ mm.

The ovum is nearly completely embedded within a rather markedly vascular but relatively ischemic endometrium showing only minimal predecidual response. The trophoblast, indifferent at the abembryonic pole, possesses elsewhere an inner cytotrophoblast and an outer, lacuna-riddled, blood-filled syncytiotrophoblast.

The nearly globular, normally situated, bilaminar germ disk shows early vacuolization of its ectoderm. The amnion is well formed but still lightly attached to its parental trophoblast. Mesoblast formation is active with development of the exocoelomic (Heuser's) membrane. Angiogenesis is absent within the chorionic cavity. Focal accumulations of cytotrophoblast — primordia of chorionic villi — are beginning to appear.

Effect of some of the B Complex vitamins upon chick tissue in cultures. Duncan C. HETHERINGTON, Department of Anatomy, Duke University.

In view of the prominence which some of the B Complex vitamins are assuming in the role of therapy especially in certain disorders resulting in alterations of the skin and nervous systems, it was thought of interest to discover whether some of these vitamins might have any effect upon chick tissue grown in vitro.

Brain and skin of ectodermal origin, and heart of mesodermal origin were cultivated by the hanging drop method in the presence of riboflavin, nicotinamide, thiamine chloride, pyridoxin, and calcium pantothenate separately in dilutions ranging from 1/500 to 1/16000. The media for control cultures consisted only of chicken plasma and Ringer's Tyrode's solution in equal parts; that for the experimental cultures was identical except that the saline contained the requisite amounts of the vitamin to be tested.

High concentrations of the vitamins in question were either toxic or suppressive in their effects. In greater dilutions the vitamin cultures grew insignificantly better than the controls except for cardiac tissue which was not stimulated at all in the presence of thiamine chloride in any of the dilutions used in the experiment. In brief it may be said that cardiac tissue was unaffected by thiamine chloride in nontoxic dilutions while brain and skin were stimulated only insignificantly by the B factors investigated.

Human brain cells in tissue cultures. Mary Jane HOGUE, Department of Anatomy, University of Pennsylvania.

Brain cells from a series of human fetuses, whose crown rump measurements varied from 27 mm. to 180 mm. have been grown in hanging drop and roller tube cultures. All of the cultures have shown migration of neuroglia cells. Nine out of fifteen fetuses have given good growths of nerve cells. So far the best growth has been in cultures from fetuses from 68 to 180 mm. long. Much depends on the condition of the fetus when received. The first cells to appear in the cultures are the small microglia cells which are active with amoeboid motion but do not live long. Later oligodendroglia, granular and Purkinje cells and many other kinds of cells not yet identified migrate out from the explanted brain tissue into the surrounding medium and form a neuropile. Cultures of nerve cells have been kept in good condition for 94 days. From stained slides we know that some of these nerve cells are dividing by mitosis.

Is acetylcholine the "synaptic transmitter" in the carotid body? W. Henry HOLLINSHEAD and Charles H. SAWYER, Department of Anatomy, Duke University.

The suggestion has repeatedly been made that acetylcholine is concerned in the initiation of carotid body reflexes. Von Euler, Liljestrand and Zotterman ('39, '41) have adduced physiological and pharmacological evidence that the role of acetylcholine is that of a synaptic transmitter, acting upon a ganglionic synapse present in the peripheral sensory path. On the basis of known anatomy, the "synapse" can only be the point of contact between the chemoreceptor cells and the sensory endings. If the "synaptic transmitter" is acetylcholine, the cells must therefore be rich in this substance.

Micromethods for determining directly the acetylcholine content of an organ the size of the cat carotid body are not available; however, there are suitable methods for determining the concentration of the cholinesterases, and there is a close correlation between the local concentration of true cholinesterase and that of acetylcholine. Employing the method used in the cholinesterase assays with sympathetic ganglia and fibers, the cholinesterase content of the carotid bodies of each of twelve cats was determined. The true cholinesterase content of this organ is very low, in marked contrast to that of organs in which acetylcholine acts as a synaptic transmitter. The results indicate, therefore, that the cholinergic mediator between chemoreceptor cell and sensory nerve fiber is not acetylcholine.

Reaction of the colon to electrical stimulation of the forebrain of the cat. E. H. INGERSOLL and Louise JONES. Department of Anatomy, Medical College of Virginia.

Using the Horsley-Clarke apparatus and bipolar electrodes with the cat under light ether anesthesia, points in the thalamus, hypothalamus, internal capsule and caudate nucleus were stimulated in 33 animals, of which 24 are reported here. The stimulating current was supplied by an electronic inductorium at a frequency of 45 osculations per second and a weak voltage of approximately 30. The responses in the lower colon, which were recorded upon kymographic records, were of three general types, namely: immediate contraction, delayed contraction and inhibition. Brains were explored from the level of the anterior commissure to points just caudal to the mammillary bodies. The immediate type of response was elicited from many levels and from the anterior and posterior portions of the hypothalamus. The delayed type of response, although obtained less frequently than the immediate response, was observed in practically all levels stimulated. Inhibition of peristalsis or relaxation of tone of the lower colon was obtained from practically all levels explored. Acute section of the cord just below the level of the sympathetic outflow seemed to modify or abolish the original response. No responses were obtained in eight of the twenty-four cats reported.

The effect of low thyroxin dosage on the thyrotrophic potency of the pars anterior of the mouse. Dorothy JENSEN, Department of Zoology, Mount Holyoke College. (Introduced by A. Elizabeth ADAMS.)

Three series of mature male albino mice were injected with 0.03 mg. of thyroxin daily for 5, 10 and 15 days respectively. The anterior pituitaries from the thyroxin-injected mice and an untreated control series were implanted into day-old White Leghorn chicks for assay of thyrotrophic potency. Chick thyroid cell height was measured 24 hours after implantation of the pituitary to determine stimulation.

Normal mouse pituitaries caused a statistically significant increase in chick thyroid cell height of 53.41% over that of untreated control chicks. Implants of pituitaries of mice receiving the lowest total dose of thyroxin (0.15 mg.) resulted in a statistically significant increase in thyroid cell height of only 4.55% over that of control chicks. Comparison of these increases showed a 91.48% decrease in thyrotrophic potency of the mouse pituitary following the thyroxin injections. Doses of 0.30 and 0.45 mg. of thyroxin gave corresponding reductions in thyrotrophin content.

Similar previous experiments involving a total dose of 0.64 mg. of thyroxin over a 21-day period reduced the thyrotrophic potency of the mouse pituitary by 92.71% (Adams and Jensen, '44). Decrease of the dosage in the present work does not appreciably change the extent of this depletion of the thyrotrophic factor. Further experiments are planned to determine the minimal dose of thyroxin effective in diminishing the thyroid-stimulating power of the pituitary.

*Changes in potency of desiccated stomach preparations due to heat and age.*¹ Oliver P. JONES, Department of Anatomy, University of Buffalo.

In the course of experiments to develop a presumptive test for antipernicious anemia principle it was thought ventriculin (Parke, Davis and Co.), because of its reported thermolability, could be inactivated by heating it in an autoclave for 20 minutes. Diets containing 2.5% of this material and regular ventriculin were fed to pregnant rats and studies of embryonic blood were conducted according to a previously described technic (Jones, '42). Control series consisted of seventy-one embryos from thirty-five rats while the test series had sixty-one embryos from thirty-two rats. Toasted ventriculin was significantly more active than regular ventriculin. However, ventriculin is definitely inactivated by either autoclaving or boiling an aqueous

¹ Aided by a grant from the Committee on Scientific Research of the American Medical Association.

suspension. Now, 4 years later, similar experiments, with a control series of twenty embryos from eight rats and a test series of fifty-seven embryos from twenty-four rats, revealed changes in potency of these preparations. Although regular ventriculin had diminished very slightly in its potency, toasted ventriculin, made from the former, was slightly more potent but not significantly more so as in the previous experiment. These results indicate that ventriculin reacts differently in the presence of dry and moist heat. The explanation for the former may be similar to the one offered by Hayward, Steenbock and Bohstedt for increased nutritive value of toasted soy bean protein. Response of pernicious anemia patients to toasted ventriculin is undetermined.

Studies on the innervation of the guinea pig heart. Cornelius T. KAYLOR, Department of Anatomy, Syracuse University.

Hearts of newborn guinea pigs were sectioned serially after staining with the Cajal silver nitrate method. This silver method gives a differential impregnation of nerve fibers. The sympathetic postganglionics appear yellow, while all other fibers stain brown to black.

In the dog, cat, and monkey heart, Nonidez ('39, '43) demonstrated that most of the deeply stained parasympathetic postganglionic fibers are distributed to structures above the coronary sulcus, i.e. atrial musculature, arteries, nodes. The lightly stained sympathetic postganglionic fibers supply chiefly the ventricles.

In the guinea pig heart, preliminary studies show that most of the deeply stained fibers (presumably parasympathetics) are distributed to the ventricles following the A-V Node, the main bundle, and the bundle branches. Whether there are nerve endings in bundle tissue and in the ventricular myocardium has not been accurately determined. The atrial musculature and vessels, and the region of the S-A Node, are sparsely supplied with deeply stained fibers. The course of the sympathetic postganglionic fibers could not easily be followed.

When the vagi are stimulated with weak currents in the anesthetized guinea pig, the electrocardiogram indicates that the ventricles are affected sooner and to a greater extent than the atria. It is therefore thought that the physiology of this heart is in accord with the anatomical distribution of presumably parasympathetic nerve fibers.

Efferent fibers of the substantia nigra in the cat. Donald L. KIMMEL, Department of Anatomy, Temple University.

Experimental studies on the substantia nigra in the cat indicate that the efferent fibers arising in this nuclear complex are distributed to the corpus striatum, hypothalamus, tegmentum and tectum. The nigrostriatal fibers ascend within the basis pedunculi and internal capsule to end in the entopeduncular nucleus and globus pallidus. Fibers to the hypothalamus course rostrally within the mammillary peduncle to terminate in the following homolateral cell groups: (1) lateral hypothalamic nucleus, (2) ventrolateral hypothalamic nucleus, (3) lateral mammillary nucleus, (4) medial mammillary nucleus and (5) supramammillary nucleus. The nigro- tegmental fibers are distributed to the homo- and contralateral red nuclei, to the contralateral substantia nigra and homolaterally to the nucleus of the medial longitudinal fasciculus, to the nucleus of the posterior commissure and to the lateral reticular nuclear groups of the mesencephalon, pons and medulla oblongata. Some degenerated fibers, which appear to originate in the substantia nigra, continue into the spinal cord. The nigrotectal fibers course dorsally through the tegmentum and enter the tectum as a component of the stratum album profundum. The majority of these fibers terminate in the homolateral tectal gray and others enter the superior colliculus of the opposite side via the commissure of the superior colliculus.

The islets of Langerhans in long term alloxan diabetes. Arthur KIRSCHBAUM and E. T. BELL, Departments of Anatomy and Pathology, University of Minnesota.

Young adult mice and albino rats were made diabetic by the subcutaneous administration of 200 milligrams of alloxan per kilogram of body weight. Diabetic ABC mice gained weight

in spite of hyperglycemia and glycosuria. In strain NH mice, however, body weight did not increase, acetonuria ultimately appeared, and the animals succumbed to the effects of the disease, usually within 100 days after the injection of alloxan. The pancreatic lesion was selective destruction of a large percentage of the beta cells.

The number of beta cells was still reduced in mice diabetic for 300 days. Alpha cells were more numerous than in normal islets. Diabetes existing 1 month after alloxan injection did not recover spontaneously. In rats, too, beta cell regeneration was lacking in untreated diabetes of 8 months' duration.

These observations indicate that spontaneous beta cell regeneration is minimal, if it occurs at all, in severe alloxan diabetes. Increase in the number of alpha cells was not effective in reducing the blood glucose to normal levels. Available evidence indicates that the beta cells are probably the primary source of insulin in these experimental animals.

Cortical connections in the rat. Wendell J. S. KRIEG, Institute of Neurology, Northwestern University.

As one aspect of a project to study the projectional and associational connections of the cerebral cortex, the brain of the albino rat is being subjected to a series of lesions, and the resulting degeneration followed in Marchi sections. Sixty lesions, mostly about a millimeter in diameter, were accurately placed in various sites of the cortex and thalamus by a stereotaxic machine designed for the rat. After 8 to 12 days the serial Marchi sections, alternately counterstained by thionin, were transformed into graphic slice reconstructions, with lesions and degenerated fiber tracts represented in phantom.

Thus far the dorsal aspect of the cortex and the medial region of the thalamus have been studied. All regions send fibers in an orderly manner into the internal capsule, and, except for the occipital region, into the peduncle. Here many categories of fibers run into tegmentum, colliculi, incerta and nigra. Fibers from a large part of the cortex persevere into the bulbar pyramids. Locations on the cortex send fibers to specific parts of the thalamus. These do not necessarily correspond with regions projecting to the cortex. There is a marked tendency to regional specificity.

Projection fibers from the medial thalamic nuclei form the anterior thalamic radiation. Nucleus parafascicularis projects to the orbital frontal cortex, nucleus medialis to the frontal pole and nuclei anterior to the medial or cingular cortex, as far as the retrosplenial region.

Connections of stria medullaris thalami. Wendell J. S. KRIEG, Institute of Neurology, Northwestern University.

In the course of making a series of minute lesions in the thalamus of the albino rat, the stria medullaris thalamic was injured in nine cases, in six of which no other diencephalic structures were touched. The resulting degeneration was studied by the Swank-Davenport modification of the Marchi method and alternate sections counterstained with thionin.

All brains, except one, where the lesion was small and medial, showed degeneration in both directions in the striae medullares of both sides. The connection across the midline was through the habenular commissure. There was no noticeable difference in number of granules of either side or in either direction. These facts indicate that the stria medullaris is to some degree commissural between the nuclear structures at its extremities.

The granules may be followed, on both sides, forwards around the rostral end of the anterior thalamic nuclei, then ventrally to the lateral part of the medial forebrain bundle. Some of the fibers curve caudally within the bundle to end at the level of the caudal part of the nucleus supraopticus (tangentialis). The granules may be followed forward to the anterior extreme of the medial forebrain bundle, to the transverse level of the nucleus olfactorius lateralis, but they never leave the territory of the bundle, hence must end in contact with the many interstitial cells of the bundle.

The effects of fatigue and curare on the morphology of the motor end plates. RAY KING, Department of Anatomy, University of Nebraska. (Introduced by W. A. WILLARD.)

Measurements were made of the motor end plates of fatigued, curarized and normal resting skeletal muscle of the albino rat. The animals used were of uniform size and age. The same part of the medial head of the gastrocnemius was, in each case, prepared by the gold chloride method and to avoid differences due to technique all material was carried through the reagents together in the same container. All plates along a nerve branch were included to insure getting a representative group.

(1) Normal unstimulated muscle: six hundred thirty-four plates from thirteen control animals were measured. The average diameter was 33.4 microns with a range of 16.6 to 73.0 microns. (2) Muscles fatigued by supermaximal tetanic stimulation for ten minutes: four hundred sixty-three plates gave an average diameter of 35.6 microns with a range of 17.4 to 64.2 microns. (3) Curarized muscle: The rats were killed by lethal doses of pure crystalline d-tubocurarine chloride. Three hundred eighty-nine plates gave an average diameter of 36.2 microns with a range of 22.0 to 76.0 microns.

The above differences are not considered significant and the results fail to support the findings of others on motor end plate morphology.

Sulphydryl groups and alloxan diabetes. ARNOLD LAZAROW, Department of Anatomy, Western Reserve University.

Since alloxan combines with the sulphydryl groups of proteins, cysteine and glutathione were tested for their effect on experimental alloxan diabetes. Neutralized solutions of cysteine and glutathione were injected into the tail vein of rats in doses of 7.5 millimoles per kilogram (912 and 2,250 m μ m. per kilogram respectively). Alloxan (200 mgm. per kg.) was injected intraperitoneally at the same time. Blood sugars were taken at the end of 48 hours and at various intervals thereafter. Control experiments were carried out using alanine, glycine, sodium succinate, and phosphate buffer in place of the sulphydryl compound. None of the ten animals treated with cysteine and alloxan, and none of three treated with glutathione and alloxan showed blood sugars greater than 200 mgm. per cent at the end of 48 hours. Five of ten control animals treated with amino acids developed 48-hour blood sugars ranging from 264-629 mgm. per cent. Most of the animals treated with sodium succinate or phosphate buffer showed very high blood sugars at the end of the second day.

These results suggest that sulphydryl compounds have a protective effect in experimental alloxan diabetes. Since, however, the incidence of diabetes with a given dose of alloxan is highly variable in different strains of rats, these experiments need to be extended to a much larger series of animals in order to rule out chance.

Recovery of spermatogenesis in mice treated with stilbestrol. J. H. LEATHEM and George BABCOCK, Jr., Department of Zoology, Rutgers University.

A marked suppression in the weights of the testes and seminal vesicles was evident when 0.002 or 0.05 mg. of stilbestrol was injected subcutaneously daily for 16 days. Spermatogenesis did not exceed the stage of secondary spermatocytes whereas control mice exhibited spermatozoa. Ten days after the last injection of 0.05 mg. there was no apparent recovery of testis weight and even after 30 days testis and seminal vesicle weights were subnormal. Spermatozoa were observed in the testes after a 20-day recovery period. Following the 0.002 mg. dosage a definite increase in testis weight was evident in 10 days at which time spermatids were seen and by 20 days a normal testis weight had been reached. Complete recovery of spermatogenic function as judged by the presence of spermatozoa in the epididymis was not attained until 30 days after cessation of injections. Seminal vesicle weight too was normal after a 20-day recovery period although no increase was apparent during the first 10 days.

Action of testosterone propionate and desoxycorticosterone acetate on adrenal weight. James H. LEATHEM, Department of Zoology, Rutgers University.

Normal and gonadectomized rats of both sexes were studied after the daily subcutaneous injection of 1 mg. of either testosterone propionate (perandren, Ciba) or desoxycorticosterone acetate (percorten, Ciba). Hormone administration was begun at 14 days of age and continued for 24 days. The injected rats were separated from their littermate controls when weaned at 21 days of age. A significant suppression of adrenal weight was observed in all injected groups. The groups of castrated males exhibited the most pronounced weight differences since the control adrenal weights were greater than those of normal rats. The injection of oil alone did not influence the control adrenal weights. The suppression of adrenal weight was not due to an influence on body weight. Desoxycorticosterone acetate did not alter the rate of body weight increase whereas testosterone propionate treated rats gained more weight than the controls.

Using 22-day-old female mice, 1 mg. of desoxycorticosterone acetate was injected daily for 20 days but adrenal weight was unchanged and the adrenal X-zone was not influenced. On the other hand, as little as 0.5 mg. of testosterone propionate in a single subcutaneous injection resulted in a loss of the adrenal X-zone and in these animals adrenal weight was 3.6 mg. as compared with 4.7 mg. in control mice.

*Axon growth and regeneration.*¹ Warren H. LEWIS, The Wistar Institute of Anatomy and Biology.

Nerve cells like most other cells and amebae probably have a superficial gel layer. It extends tube-like along axon and over ameboid end. Continuous contractile tension of gel layer over cell body forces endoplasm along axon tube into expanding end where gel layer is weaker. Here endoplasm gels at the surface. Gel layer at base of end is older and thicker and progressively contracts to axon size and lengthens the latter while the tip keeps expanding. It is here at the base of ameboid ends and here only that axons increase in length. There is no interstitial increase in length of axon between cell body and ameboid end. Cytoplasmic synthesis occurs mostly in cell body. Gel layer is not visible. Ameboid end lengthens like an ameba pseudopod.

In cultures axons frequently extend along coverglass and cross at approximately right angles. Contact zones are never pulled toward the ameboid end. The angle of a lateral branch with main axon does not alter as the latter increases in length. They are not pulled along. Motion pictures show that axons have curves that are continually changing indicating local increases and decreases of contractile tension of their gel layers. Ameboid tips like other pseudopodia frequently pinocytose.

Above theory explains damming effect obtained by Weiss, Biol. Bull. 87: 160.

¹ Aided by a grant from The John and Mary R. Markle Foundation.

The relationship of muscle fibers, tendon and reticulum at the muscle-tendon attachment in fetal and young rats. Margaret E. LONG, Department of Anatomy, University of Alabama. (Introduced by Thomas E. HUNT.)

Hind limb muscles, especially quadriceps femoris and triceps surae, were studied in animals of fetal and post partum stages. The muscles were dissected and oriented to give longitudinal alignment of muscle fibers and tendon. Paraffin sections were silvered by a modification of Bielchowsky's method for reticulum and counterstained with axocarmine and fast or light green.

In the 19-day fetus, fine argyrophil fibers surround each muscle fiber and appear continuous with argentofibrillae of tendons of attachment. The fibers of such tendons are all argyrophilic. No collagenous fibers are apparent. Tendon fibers are continuous with fibrous matrix of cartilages (patella or calcaneus) into which they insert.

At birth and 2 days, these argyrophil tendon fibers are thicker and take on a greenish tinge indicating the presence of collagen. The delicate silvered reticulum immediately adherent to the sarcolemma is continuous with the fine argyrophil fibrillae of the tendon, which in turn become the thicker collagenous fibers. At 2 days, also, argyrophil projections invaginate the ends of muscle fibers.

The axocarmine counterstain makes it possible to distinguish the cross striated myofibrillae in fetal and adult material, at the tendinous attachment, as well as throughout the fiber. The myofibrillae are clearly distinguishable from the argyrophilic reticulum. A study of the relation of the sarcolemma to this subject in a complete series of younger and older stages is in progress.

Further evidence for the vital necessity of adrenal cortical tissue in a mammal. W. E. MacFARLAND, Department of Anatomy, Chicago Medical School. (Introduced by J. J. SHEININ.)

Adrenal cortical tissue appears to be necessary for survival in mammals, even under laboratory conditions not conducive to stress. Of the various factors modifying the survival period of adrenalectomized animals, the proliferation of "microscopically indifferent" tissue is important.

In fifty-three albino rats, two basic approaches were, (1) bilateral adrenalectomy, one and two stage operations, and, (2) autoplasmic transplantation of whole adrenals subcutaneously, unilaterally or bilaterally, followed, in cases of survival, by removal of transplants.

Abrupt removal of all cortical tissue resulted in death. Likewise, those animals in which the transplants failed to take, died within two weeks. Functional transplants helped to maintain the other animals in good conditions. Removal of these transplants usually resulted in death after varying periods of survival up to six weeks. Some even survived this last operation indefinitely. In these instances, cortical tissue was found near the normal adrenal sites. That this tissue had proliferated from dormant cells resembling fibroblasts was concluded chiefly because, (1) the cortical cells were distributed diffusely as small islets in a web of "capsular" tissue, a condition rarely seen for accessory cortical bodies, and, (2) some intermediate cell types could be distinguished.

The marginal and partitional types of base in mammalian pulmonic alveoli. Charles C. MACKLIN, University of Western Ontario.

Alveolar bases were classified in lungs from eleven mammalian species — man, goat, pig, dog, baboon, monkey, cat, rabbit, guinea pig, rat and mouse. Fixation at approximately normal inflation was by vascular perfusion in the unopened thorax or by tracheal injection with control of degree of distention by thoracic measurements. Microsections of varying thickness and staining, from all seven pulmonic lobes or corresponding regions, showed in each axially sectioned alveolus either (1) the "marginal" type of base, resting on connective tissue of a blood vessel, bronchus, pleura or interlobular partition; or (2) the "partitional" type, separating adjoining alveoli, and supported by only a minimum of connective tissue. A row of partitional bases often appears as a zigzag line. The marginal type has but one functional surface, whereas the partitional type, with air on both sides, has two. The marginal bases usually bear more epicytes than do the partitional. Pathologically considered, the most important difference is in the result of rupture from undue air pressure, which has been studied experimentally, particularly in the cat. Through minute and often multiple leakholes so produced in marginal bases, air enters the interstitial connective tissue, causing pulmonic "interstitial emphysema", and may spread to the mediastinum, producing "pneumomediastinum", sometimes involving serious or even fatal interference with circulation and respiration from pressure of air bubbles. Rupture of partitional bases has no such consequences.

Is iron stored normally in large quantities in human fetal livers? Madge Thurlow MACKLIN, University of Western Ontario. (Introduced by C. C. MACKLIN.)

It has been claimed that excess quantities of iron are stored in fetal liver in preparation for postnatal dearth of iron in maternal milk. Sections of one hundred thirty-nine fetal livers, ranging from 11 weeks to term, were treated by the Prussian Blue technic for demonstration of organic or inorganic iron. Iron although present in one fetus as early as 11 weeks, was not found in 60% of the livers which covered the whole age range examined. Iron in granular form in Kupffer cells, sometimes in liver cells, was present in 33%, and diffuse staining at edges of red blood cells in 7%.

These findings suggest that iron in quantities demonstrable by the Prussian Blue technic is not normally present in fetal liver, even at or just before term. Iron, when present, appears to indicate undue hemolysis in the fetus, and correlation with other work shows that antibodies due to Rh incompatibility between mother and fetus and circulating in the fetus, is a common cause of hemolysis. We suggest that perhaps the finding of large amounts of iron in fetal livers, and interpreted as a physiologic storage process, has been caused by the examination of fetuses dying as a result of Rh incompatibility, a not infrequent cause of fetal death.

An inhibitory mechanism in the bulbar reticular formation. H. W. MAGOUN and R. RHINES, Department of Anatomy, Northwestern University.

Electrical stimulation of the lower brain stem of the cat has revealed a bulbar mechanism capable of widespread inhibition of existing motor activity. This mechanism is effective against spinal and cranial reflexes, decerebrate rigidity, and activity induced from the motor cortex. The excitable inhibitory area is distributed chiefly in the ventral-medial portion of the bulbar reticular formation and extends at least as far forward as the caudal end of the pons. The inhibitory effects induced by its stimulation are frequently followed by a subsequent augmentation of whatever activity is proceeding and purely facilitatory influences are often evoked from the periphery of the field.

Both inhibitory and facilitatory effects upon spinal reflexes and upon responses from the motor cortex have also been obtained from stimulating the lower brain stem reticular formation in the monkey, but work on this animal is still in a preliminary stage.

The position of this bulbar mechanism plus the demonstration of connections to it from cortical area 4-S (see McCulloch, Graf and Magoun) suggest that it represents an immediate pre-spinal station in the extra-pyramidal motor system.

*Plurisegmental innervation and muscular contraction.*¹ J. E. MARKEE and Hans LÖWENBACH, Departments of Anatomy, Physiology and Neuropsychiatry, Duke University.

Using photographic procedures, contractions of the rectus femoris, biceps femoris, semitendinosus and semimembranosus muscles were recorded and analyzed in twenty-six dogs. The first results were reported in the Federation Proceedings, 1945.

With indirect electrical stimulation isometric and isotonic contraction in variable ratio occurs simultaneously in different "segments" of the same muscle. With direct stimulation the part stimulated shortens and the remainder stretches considerably. A similar result is obtained by stimulation of only one of the main branches of the supplying nerve.

When the main branches of the nerve are carefully separated from each other as far centrally as the nerve trunk, stimulation of the branches at this point still produces a shortening of that part of the muscle innervated by this branch. These branches are not formed by dichotomy but constitute separate "strands" in a common sheath.

¹ Aided by a grant from the National Foundation for Infantile Paralysis, Inc.

Stimulation of the appropriate ventral spinal roots produces "segmental" contraction of the muscles studied. Stimulation of a more cranial root produces contraction of the more proximal "segments" of a muscle and stimulation of a more caudal root produces contraction of a more distal part of this muscle. Thus, the segmental innervation of a muscle seems to be arranged in a definite order, the more cranial spinal root reaching the muscle through the proximal branch ("strand") of the nerve.

Does the ventral funiculus of the rhesus contain uncrossed pyramidal fibers. Fred A METTLER, Department of Neurology, College of Physicians and Surgeons, Columbia University.

It is possible (J. Comp. Neur., v. 80, p. 147) to place lesions in the presumptive course of the pyramidal system without producing detectable degeneration in the homolateral ventral spinal funiculus. Professor A. T. Rasmussen recently sent me some material from a monkey from which Professor Campbell had removed Brodmann's area 4. There was definite degeneration in the homolateral ventral funiculus. Dr. Campbell later wrote that another case, from which the ventral portion of Brodmann's area 4 had been removed, had failed to substantiate the findings of the first and suggested that the uncrossed fibers might have a very restricted origin.

This hypothesis was tested by removing that part of the precentral gyrus between the arcuate and central fissures from the left side of a rhesus (J 182 T) and the dorsal half of area 4 from the right side. The spinal cord showed abundant degeneration of the left lateral corticospinal tract, slight of the right and some slight degeneration (proceeding to the junction between L I-II) in the right ventral funiculus.

More significantly, Marchi sections through the medullary pyramids disclosed little degeneration in any part of the left. Silver sections showed no more. Since the left lesion comprehended the ventral half of Brodmann's area 4 it is apparent that this sends few if any fibers into the cord. These findings are in better agreement with Bonin's than Brodmann's map.

*The modus operandi of the developmental potential underlying the varied arterial blood supply of the liver and gall bladder.*¹ Nicholas A. MICHELS, Daniel Baugh Institute of Anatomy, Jefferson Medical College.

Typically the hepatic after giving off the gastroduodenal divides into the right, middle and left hepatic, the middle hepatic (for quadrate lobe) being a branch of either the right or left hepatic. This pattern prevails in about half of the bodies (sample of 100 of the 165 bodies investigated), in others variations obtain for the following reasons:

1. When the hepatic divides into the gastroduodenal and right hepatic, the left hepatic (and its middle hepatic branch) is replaced by an artery from the left gastric (11%).
2. When the hepatic divides into the gastroduodenal and left hepatic, the right hepatic (and its middle hepatic) is replaced by an artery from the superior mesenteric or celiac trunk (10%).
3. Occasionally the hepatic divides into the gastroduodenal and middle hepatic, both right and left hepatics being replaced.

Such replacing hepatics should henceforth not be called accessory right or left hepatics since functionally they are definitely not accessory but the main right or left hepatics, i.e., they are replaced hepatics. An accessory hepatic from the left gastric (13%) or superior mesenteric (10%) occurs only in conjunction with a typical left or right celiac hepatic, i.e., when either of the latter is small, one accessory hepatic is present, when both are small two accessory hepatics (right and left) are present. A body may have 5 hepatics (3 from the hepatic trunk, 1 from the superior mesenteric and 1 from the left gastric).

¹ Aided by a grant from the American Philosophical Society.

*The dorsal pancreatic and transverse pancreatic arteries.*¹ Nicholas A. MICHELS, Daniel Baugh Institute of Anatomy, Jefferson Medical College.

1. The dorsal pancreatic (superior pancreatic), 1-5 mm. in diameter, is distributed to the posterior surface of the neck of the pancreas and to the uncinate process. Usually it arises from the celiac (tetrapod) or the first part of either the splenic or hepatic. Otherwise, it comes from the superior mesenteric, middle colic, accessory or replacing right hepatic, or aorta. Passing either dorsal or ventral to the splenic vein it terminates in: (a) left branch (transverse pancreatic); (b) right branch which unites variously with the gastroduodenal, superior pancreaticoduodenal, right gastroepiploic or inferior pancreaticoduodenal. The dorsal pancreatic may give rise to the right, left or middle colic. The branch which supplies the uncinate process invariably passes behind the portal vein.

2. The transverse pancreatic (inferior pancreatic), 1-5 mm. in diameter, nearly always courses along the inferior (dorsal) border of the pancreas, from the neck of the organ to its tail. Here it anastomoses with a branch of the a. pancreatica magna from the splenic trunk or with the a. caudae pancreatis from a lower splenic terminal. In most instances the transverse pancreatic is the prominent left branch of the dorsal pancreatic. Other sites of its origin are: the gastroduodenal, superior pancreaticoduodenal, right gastroepiploic, inferior pancreaticoduodenal and superior mesenteric. It may be sufficiently large to constitute an a. splenica secunda to the spleen. Its posterior epiploic branches (1-5) course through the transverse mesocolon providing the transverse colon with an added blood supply.

¹ Aided by a grant from the American Philosophical Society.

An anomalous pulmonary vein draining the left superior lobe. Photis J. NICHOLS and E. Reed GASKIN, Department of Anatomy, Emory University. (Introduced by Homer BLINCOE.)

An anomalous vein that originated from the superior lobe of the left lung and terminated in the distal end of the left innominate vein was found in routine class dissection. In the lung it was formed by the confluence of four veins: three from the superior lobe (constituting its entire venous drainage), and a fourth from the posterior portion of a partially separated middle lobe. The body was that of a negro male, age 53, who died of typhus fever.

This vein runs vertically and a little anteriorly, immediately under cover of the mediastinal pleura. Its length is 5 cm. and its diameter 1.2 cm. Its tributaries are: (1) the left superior intercostal vein and (2) the left pericardiac vein.

The pulmonary artery appears normal, supplying the entire lung. No bronchial veins were found. Two left pulmonary veins enter the heart, one from the ventro-lateral portion of the left middle lobe, and one from the inferior lobe. The heart was dilated, but only slightly hypertrophied.

All the blood that entered the left superior lobe must have returned to the systemic veins and thence to the right heart and back to the lungs.

The best explanation of this anomaly seems to be the unusual development of a bronchial vein which has substituted for the pulmonary branch from the left superior lobe.

Nuclear masses of amygdala of chimpanzee, from graphic reconstructions. William T. NIEMER and James W. PAPEZ, Department of Zoology, Cornell University.

The amygdala forms a rounded mass in tip of temporal horn; rotated medially so that it lies ventral to optic tract. Its medial surface is formed by lateral olfactory nucleus and cortical nucleus of amygdala. Beneath latter are three thickened strata of cells forming large accessory, basal and lateral amygdaloid nuclei. Each nucleus has a medial and a ventro-lateral surface. The accessory is beneath cortical nucleus; basal is bent around outer surface of accessory; and lateral is bent around basal, its posterior surface contacting lateral

ventricle and hippocampus. Each nucleus has two parts and two borders. Medial borders contact cortex; that of accessory nucleus contacts cortical nucleus; that of basal contacts transitional area at amygdalar fissure; lateral contacts pyriform cortex below amygdalar fissure. The dorsal parts and borders are more separated by fibers. Here, fibers of inferior thalamic peduncle enter from front and spread to accessory, basal and lateral nuclei. Anterior cellular area is bed nucleus among these fibers; and small intercalated nuclei occur among fibers between other nuclei. Fibers leave main nuclei at their dorsal borders to enter terminal stria. They surround an oval central nucleus which contributes fibers to stria. Lateral nucleus contributes fibers to anterior commissure. Nucleus of lateral olfactory tract is at dorsal medial surface. Deep to it is the medial nucleus. Basal claustral complex underlies pyriform and mainly anterior pyriform cortex.

Angiogenesis in the amnionic mesoderm of a baboon embryo. Charles R. NOBACK, Department of Anatomy, Long Island College of Medicine.

Angiogenesis in the amnion of an estimated 26-day-old baboon embryo is evidenced by the presence of blood islands and vascular spaces in the amnionic mesoderm.

These islands are in five elongated anastomotic cords which radiate from the body stalk in the region of the amnio-body wall junction into the amnion. Using the orientation of the embryo as it floats in the amnionic sac as a reference, three of these five cords extend cephalically and the other two cords extend caudally almost to the cephalic and caudal poles of the amnion respectively. The three cephalic cords are oriented on the amnion as follows: the first cord is on the right dorso-lateral aspect, the second cord is on the right ventro-lateral aspect and the third cord is on the left dorso-lateral aspect. The two caudal cords are oriented on the amnion as follows: the first cord is on the right dorso-lateral aspect and the second cord is on the left ventro-lateral aspect. There is no demonstrable continuity of these cords with any of the body wall or body stalk blood vessels. Only in the region of the amnio-body wall junction in the amnion proper do these five cords interanastomose with each other.

From this observation and a few in the literature it may be concluded that the amnionic mesoderm can have angiogenetic potentialities.

The etiology and inheritance of inequalities in the jaws of sheep. Julius E. NORDBY, Clair E. TERRILL, Lancy N. HAZEL and John A. STOEHR, Bureau of Animal Industry, Agricultural Research Administration, U. S. Department of Agriculture.

Sheep with overshot jaws (upper jaw longer than lower) had longer skulls and shorter mandibles than normal animals. Abnormal mandibles were shortened along their entire length, but the space occupied by the molar teeth was shortened least. The maxilla was the only structure of the upper jaw that was appreciably longer in overshot ewes. Inequality of the jaws increased from birth to weaning to yearling age. Linear skull measurements were more variable in overshot than in normal animals. However, positive correlations were found between upper and lower jaw structures in both overshot and normal groups. A tendency was apparent in normal, but not in overshot, animals for the angles of the incisor teeth to compensate for slight jaw inequalities. These angles in normal sheep were inversely correlated with mandible length and were much more variable than in overshot animals.

Overshot jaws occurred in 1.4% of the offspring from a large flock of normal Rambouillet sheep. Experimental matings in which one or both parents were overshot produced 16.4% defective offspring. The frequency of overshot offspring from matings of normal relatives suggested a simple recessive inheritance. However, matings of defective parents produced too few defective offspring to support this hypothesis. The frequency of defective offspring from such matings was found to increase with relationship between parents. Interactions of several pairs of genes were probably involved.

Conversion of prothrombin to thrombin in concentrated sucrose solution. William F. ORR, Jr. and Mary E. GRAY, Department of Medicine and Department of Anatomy, Vanderbilt University.

Purified prothrombin can be converted slowly into thrombin without the addition of calcium or thromboplastin by dissolving it in saturated sucrose solution. The reaction occurs even in low concentration of prothrombin. The yield by this method is high as the sucrose prevents the breakdown of the formed thrombin.

Comparison of the toxicity of antiseptics for embryonic tissue and bacteria. George H. PAFF, Robert A. LEHMAN and Jacob P. HALPERIN, Department of Anatomy, Long Island College of Medicine and the Department of Therapeutics, New York University.

Using the roller tube method of cultivating tissue in vitro technique has been devised for quantitative comparison under identical physiological conditions of the toxicity of antiseptics for tissue and bacteria. The procedure is simple and the results are reproducible. With fragments of 9-day embryonic chick ventricles and staphylococcus aureus the toxicity indices were found to be as follows: iodine, 0.29; azochloramide, 0.64; phenol, 2.7; zephiran, 3.4; merthiolate, 3.9; saponated solution of cresol U.S.P. XII, 4.1; lysol, 4.3; saponated solution of o-hydroxydiphenyl, 12.5. Under the conditions employed, the larger the value, the less desirable is the antiseptic.

Some characteristic changes in the consistency of the uterine secretion. George N. PAPANICOLAOU, Department of Anatomy, Cornell University Medical College.

By fixing human vaginal, endocervical or endometrial smears in silver nitrate, it has been possible to demonstrate the presence of a characteristic brown-staining secretion. This appears to be more abundant and conspicuous at about the peak of the follicular phase. Its consistency and form change and it tends to become scantier after ovulation. It is usually very much reduced in amount or practically absent during the other phases of the cycle and in inactive states, as amenorrhea or menopause. Its relation to follicular activity is proven by the fact that it can be induced or increased experimentally by estrogenic therapy.

The origin and the chemical nature of this substance are still obscure. It is likely that it is secreted by the cervical glands. Its abundance coincides with an increased cervical secretory activity and a change in the viscosity of the cervical mucus. However, it has a distinctive appearance and shows a specificity in the staining which differs from that of the ordinary cervical mucus. Contrary to ordinary mucus, it is destroyed by fixation in alcohol-ether.

Smears fixed in silver nitrate can be stained with haematoxylin and an alcoholic stain like EA36 without loss of this substance. Such smears are of specific value in the study of the normal cycle and the evaluation of follicular activity and estrogenic action.

Subthalamic decussation, its origin in subthalamic nucleus and ending on the frontal end of the opposite red nucleus. James W. PAPEZ, Department of Zoology, Cornell University.

Fibers arising from cells of subthalamic nucleus or corpus of Luys form two tracts. (1) Subthalamic or supramammillary decussation. These fibers arise from cells of subthalamic nucleus, assemble on its dorsomedial surface, pass medially as diffuse fascicles looping ventrally through hypothalamic descending tract, then they curve dorsally over mammillary body to enter compact part of subthalamic decussation through which they reach front end of opposite red nucleus. Serial sections from four human brains with lesions in front of red nucleus, in decussation and in subthalamic nuclei were used to verify description and polarity of these fibers. (2) Subthalamico-tegmental tract is not crossed. Its fibers arise from cells of subthalamic nucleus, assemble in dorsomedial surface, pass down in curve ventral and lateral to

red nucleus, then turn dorsally, pierce medial lemniscus and end in lateral tegmental nucleus of midbrain.

(3) A large tract of fibers, associated with dorsal supraoptic decussation close to medial longitudinal fasciculus, passes over dorsomedial surface of red nucleus and crosses prerubral field to reach dorsomedial hypothalamic nucleus, zona incerta and reticular nucleus of thalamus. It has no sure connections with red nucleus. (4) Fasciculus geniculatus descendens arises from ventral part of lateral geniculate body, passes medially, dorsal to subthalamic nucleus, and caudally to end in a distinct part of substantia nigra. Reduced in primates. It has no connection with red nucleus.

Fiber tracts of the amygdaloid region in the human brain, from a graphic reconstruction of fiber connections and nuclear masses. James W. PAPEZ, Department of Zoology, Cornell University.

(1) A large tract of fibers enters amygdaloid region from front as continuation of inferior thalamic peduncle via anterior perforated substance. It turns ventrally and posteriorly, medial to basal claustral complex, to enter anterior amygdaloid area. Here its fibers spread and surround dorsal borders of lateral, basal and accessory basal nuclei depositing within them much neuropil. The two parts of basal and accessory basal receive separate contingents of such fibers. (2) A part of inferior thalamic peduncle passes laterally through basal claustral complex to enter white matter of temporal pole. (3) Lateral olfactory tract passing in superficial layer is related to lateral olfactory nucleus, and this to basal claustral complex and medial amygdaloid nucleus. (4) Five bands of terminal stria issue from lateral, basal, accessory, medial and central nuclei. Passing dorsolaterally they enclose central nucleus and enter tail of caudate. (5) Some fibers from lateral pass to anterior commissure. (6) Fiber strata deep to cortical nucleus are related to cell clusters in medial part of accessory basal nucleus; others to medial nucleus. (7) Some fibers deep to pyriform cortex at transition area are related to medial (deep) part of basal nucleus. (8) Fibers from pyriform cortex pass around deep frontal surface of amygdala to claustrum. (9) Some bundles of optic radiations turn down through frontal part of lateral nucleus. (10) Uncinate fasciculus and anterior commissure pass through basal claustral complex.

Circulation of lymph within the liver lobule. Paul R. PATEK, Department of Anatomy, Washington University.¹

The quartz rod method of transillumination in the living animal (Knisely) was used to study the circulation of extravascular fluid in the liver lobule. A large number of dyes known to be absorbed by lymphatics were injected either intravenously, intramuscularly, into the portal vein, or into the small intestine in a series of sixty-one mice. Histologic preparations were made of those specimens which seemed most promising in vivo.

Diffusion of dye from the hepatic sinusoids into the tissue fluid of the lobule was visible only as a gradual appearance of color. No streaming was observed. Although the lymphatics leaving the liver were colored by the absorbed dye, no special lymphatic pathway could be observed within the liver lobule. Streaming, intensity of color, or other evidence for lymph flow within the supposed perisinusoidal spaces was not observed.

¹ On leave from The University of Southern California, School of Medicine.

Observations on the roots of the facial nerve in human fetuses. Anthony A. PEARSON, Baylor University.

The portion of the facial nerve immediately central to the geniculate ganglion lies in close relation to the superior division of the vestibular nerve. Part of the geniculate ganglion

may lie within the internal auditory meatus close to the vestibular ganglion. The number of cells in this part of the geniculate ganglion is variable.

Fibers which form the nervus intermedius join the vestibular nerve in the medial end of the internal auditory meatus and they often leave that nerve in several bundles. The more dorsally placed bundles enter the medulla close under the vestibular nerve and they can be followed dorsomedially among the fibers of the spinal tract of V. Sagittal sections reveal that some of these fibers turn rostrally and join fibers which continue into the caudal end of the mesencephalic tract of V. Other fibers are either lost among the fibers of the spinal tract of V and its nucleus or continue dorsomedially to enter the rostral end of the fasciculus solitarius. The more ventrally placed bundles of the nervus intermedius pass medial to the spinal tract of V and turn caudally as they enter the fasciculus solitarius. A few fibers were observed to turn rostrally. In certain fetuses, fibers of nervus intermedius continue medial to the fasciculus solitarius and join the fibers that form the internal genu of the facial nerve.

Induction of ovulation in the rhesus monkey. Carroll A. PFEIFFER, Department of Anatomy, Yale University.

In trying to induce ovulation in the rhesus monkey by injection of gonadotrophins it is a common experience to get either numerous cystic follicles or a single large cystic follicle with some development of smaller follicles. Ovulation or luteinization rarely occur. The possibility that there might be a definite period in follicular development at which injection of gonadotrophins would cause ovulation was tested on monkeys during the summer months, when they run predominantly anovulatory cycles. Seven of eight monkeys started on the sixth and eighth days of the cycle with 5 daily intravenous injections of 125 I.U. of purified pregnant mare serum (gonadin) had ovulated by the day after cessation of treatment. When treatment was started later (5 cases) the maturing follicle became large and cystic. When begun earlier (4 cases) numerous follicles rapidly enlarged but even with continued treatment failed to ovulate and became cystic. It seems unlikely that the animals started on the sixth to eighth days ovulated by chance and that the others did not. Attempts to cause ovulation by intrafollicular injection of gonadin failed, apparently because the hormone was removed too rapidly. It would seem that the follicle must be grown at a relatively slow rate until it reaches a certain critical period when there must be a proper balance between F.S.H. and L.H. or ovulation will not occur.

Effect of thymectomy in rats on lymph nodes and spleen. William O. REINHARDT, Division of Anatomy and Institute of Experimental Biology, University of California, Berkeley.

Male rats of the Long-Evans strain were thymectomized on the day following birth and autopsied at the age of 63 days together with a similar group of sham operated littermate controls. The animals were maintained on the regular laboratory diet under identical environmental conditions. At autopsy, the spleen, cervical and mesenteric lymph nodes were dissected out and weighed, identical dissections being carried out in thymectomized and control animals. The mediastina of the thymectomized rats were examined carefully for thymic remnants. The autopsy body weight of eight completely thymectomized rats averaged 233 gm., of thirteen control animals, 235 gm. There was a 30% decrease in the weight of the cervical lymph nodes and a 20% decrease in the weight of the mesenteric lymph nodes of the thymectomized as compared with the control rats. These differences in weight although small are statistically significant as indicated by critical ratios of 3.56 and 2.95 for cervical and mesenteric lymph node weights, respectively. There was no difference in the weights of the spleens in the two groups. The above experimental findings have been confirmed in other groups of male and female rats thymectomized at other ages. These findings are presented because they represent the only gross changes detected in a study of the organs and tissues of the thymectomized rat.

Thymus, lymph nodes and spleen in experimental hyperthyroidism. William O. REINHARDT, Division of Anatomy and Institute of Experimental Biology, University of California, Berkeley.

Splenic and lymph node hypertrophy have been noted in rats treated with desiccated thyroid or thyroxin. Such treatment has not, however, affected the size of the thymus gland. Since an enlarged thymus gland is frequently noted in clinical hyperthyroidism (Graves' disease), the following experiments were undertaken to show a possible relationship between the effect of experimental hyperthyroidism and thymic enlargement. Desiccated thyroid was fed to, or thyroxin was injected into, normal, adrenalectomized, partially adrenalectomized, castrated, and adrenalectomized-castrated male and female rats, for periods of 10-51 days. The thyroid treated animals were compared at autopsy with untreated operated and normal controls. The animals were maintained on 1% sodium chloride solution as drinking water. Thymus, lymph nodes and spleen were weighed at the time of autopsy. It was found that thyroid feeding or thyroxin injection increased the weight of these tissues over that of the untreated operated control animals. The thymus, spleen and lymph nodes of the thyroid treated adrenalectomized and castrated animals were twice the weight of the untreated normal animal and heavier than those of the adrenalectomized-castrated controls. These findings lend support to the hypothesis that the enlarged thymus, lymph nodes and spleen, and lymphocytosis, in Graves' disease, may be, in part, the result of an underlying partial adrenal cortical or gonadal deficiency.

*The bulbar inhibitory mechanism in concussion.*¹ R. RHINES, Department of Anatomy, Northwestern University.

The widespread impairment of reflexes in concussion may be explained either by alterations in individual reflex arcs or by alterations in a common brain mechanism influencing reflex activity. Demonstration of a bulbar mechanism with such potentialities (see Magoun and Rhines) led to an examination of its involvement in concussion (cat).

The patellar reflex was employed as a test object, and concussion was induced by a blow to a fluid column communicating with the interior of the cranium. An extensor jerk of the leg was often observed at the blow and was briefly followed in many instances by a depression and rarely by an arrest of the reflex. In most cases an augmentation of the patellar reflex, lasting from 30 seconds to 3 minutes, and independent of anoxia and the liberation of adrenalin, then preceded its return to normal.

The threshold for inhibition of the patellar reflex provided a measure of the excitability of the bulbar mechanism mentioned. Immediately after concussion its excitability remained at the control level. It was then greatly depressed and only gradually returned to normal 3 to 5 minutes later.

While variations in the excitability of the bulbar mechanism in general paralleled variations in the patellar reflex in concussion, synchrony was not precise enough to indicate that the effects of concussion should be attributed to its influence on this single brain mechanism.

¹ Work done under contract with the Office of Scientific Research and Development. Permission to publish this paper has been granted by the Committee on Medical Research, A. N. Richards, Chairman.

Initial rate of emptying of stomach in peptic ulcer patients as related to evacuation of the gall bladder. Leo G. RIGLER and Edward A. BOYDEN, Departments of Radiology and Anatomy, University of Minnesota.

Fluoroscopic observation of eighteen patients with uncomplicated duodenal ulcer and of seventeen male controls (following earlier studies on eighteen primigravidae and on seventeen female controls, Boyden and Rigler, '44) have yielded the following results. (1) The sex differences in the rate of emptying of the human gall bladder cannot be attributed to the ini-

tial rate at which a hormone-inducing meal is discharged into the duodenum, for in thirteen female students the average time of the first spurt of chyme containing egg yolk, milk and barium was 2.06 minutes as against 1.95 minutes for seventeen male students. Within the first 5.5 minutes the female stomachs discharged an estimated average of 8.1 cc. in an average of 3.2 minutes, and the male stomachs 9.2 cc. in 3.2 minutes. Incidentally, the amount in the duodenum necessary for evacuation of two-thirds to three-quarters of the contents of the gall bladder is only 10 cc. ($\frac{2}{3}$ of a swallow). (2) In seventeen patients with duodenal ulcers the average time of the first spurt was 1.56 minutes, and in the first six gastric ulcer patients 1.27 minutes. This corresponds to the faster emptying of the gall bladder in ulcer patients (Boyden and Berman, '37). (3) After the initial spurt of egg yolk the stomach is inhibited for a longer period in ulcer patients than in the controls — a fact of interest in relation to recent enterogastrone therapy.

Cholinesterase in sympathetic fibers and ganglia. Charles H. SAWYER and W. Henry HOLINSHEAD, Department of Anatomy, Duke University.

A histochemical study of the cholinesterase (ChE) of the cat cervical sympathetic trunk and superior cervical sympathetic ganglion reveals a mixture of true ChE and pseudo-ChE in both fibers and ganglion. In the ganglion the two esterases are present in strong, equal, concentrations, and both are most active in the region where preganglionic endings and ganglion cells are most concentrated. In the trunk true ChE is present in much greater amounts than pseudo-ChE.

After preganglionic section the ganglion and degenerating preganglionic fibers lose true ChE at the same rate, suggesting that their common elements, preganglionic axons and endings, produce the enzyme. Ganglionic pseudo-ChE is lost at a much slower rate than true ChE, suggesting its production by some intrinsic element less affected by the operation, perhaps ganglion cells. Stripping the ganglion to produce chromatolysis resulted in greater damage, through trauma or ischaemia, to the preganglionic endings (which disappeared altogether) than to the ganglion cells themselves. Correlated with this was a total disappearance of true ChE and a marked reduction in pseudo-ChE content.

Pseudo-ChE is lacking in the superior cervical ganglion of the guinea pig, whereas true ChE is present in amounts approximately the same as in the cat. Its distribution and localization emphasizes the importance of true ChE in synaptic transmission, whereas doubt is cast on the physiological significance of pseudo-ChE.

The occurrence of terminal loops and capillary networks in cartilage. Ernst SCHARRER, Department of Anatomy, Western Reserve University.

In the course of a study of vascular patterns of various tissues in different animals blood vessels were observed in certain types of cartilage. The cartilage of the lower jaw of the clear-nosed skate (*Raja eglanteria*) is supplied by paired vessels which end in hairpin-like loops. By contrast, the cartilage in the head of the squid (*Loligo pealii*) is vascularized by single vessels which anastomose to form a continuous capillary network. These are the same two types of blood vessels which occur in the brains of vertebrates and invertebrates. With respect to the brain two opposing views exist as to the factors determining the capillary type. According to one the blood vessels develop in these two different ways on account of differences in structural or chemical organization of the brain tissue of different species. The other maintains that the factors determining the capillary type are inherent in the vascular system itself rather than in the tissue which it supplies. The observation of paired loops and capillary networks in a tissue as different from the brain as cartilage seems to support the latter interpretation. Otherwise chemical or structural relationships between cartilage and brain tissue would have to be assumed which have not been demonstrated.

The identification of early cells of the myeloid series. Joseph L. SCHWIND, Department of Anatomy, Albany Medical College, Union University.

The blood cells of a congenital myeloblastic leukemia were studied with Wright's stain, supravital and peroxidase methods. With Wright's stain, 43.0%–51.5% were myeloblasts, 9.0%–16.0% having an acidophilic spot in the cytoplasm; 4.5%–15.0% were leucoblasts, 0.5%–5.0% having an acidophilic spot. With supravital stain, 21.6%–34.0% were myeloblasts, containing red vacuoles, while 23.6%–30.5% were myelocytes A containing vacuoles and a small cluster of neutrophilic granules. The positive peroxidase count was 5.0%–8.0%.

It is concluded (1) myeloblasts may contain neutral red vacuoles (2) neutrophilic granules can be seen in some cells with the supravital technique before an acidophilic spot or discrete neutrophil granules can be demonstrated with Romanowsky stains, and therefore for this type of work supravital staining is more advantageous (3) some Romanowsky "myeloblasts" and "leucoblasts" are actually promyelocytes, as they contain neutrophilic granules demonstrable by supravital staining (4) myeloblasts and early promyelocytes are peroxidase negative (5) myelocyte A is peroxidase negative and not positive as has been supposed (6) the usefulness of recognizing a leucoblast stage in myeloid development is questionable (7) any peroxidase positive myeloid cell already has specific granules in its cytoplasm (8) early cells of the myeloid and lymphoid series can be distinguished more dependably by careful study of Romanowsky films than by peroxidase staining.

Course of the facial nerve through the parotid gland. Cleveland S. SIMKINS, The Creighton University.

In the study of the facial nerve and its passage through the parotid gland it was found that a superior and inferior cord was formed in 73.7% of times and a plexus where slight interconnection took place 26.3%. In only 5.2% did the nerve divide the gland completely into deep and superficial lobes and no lobe formation at all was encountered 94.8% of instances. The nerve ran deep to the gland, 23.7%, within the fascial sheath, 22.3% and wholly or partially infolded by laps or layers of glandular tissue, 54%.

From the fact that a superior and an inferior cord was found so frequently and that the superior cord carried filaments to the facial muscles above the corner of the mouth and the superior cord lay invariably deep, total removal of the parotid surgically can be accomplished with relatively slight risk of permanent palsy of lower facial muscles (mentalis, platysma and quadratus labii inferioris).

Formation of the inguinal canal. Cleveland S. SIMKINS, The Creighton University.

From a study of human embryos and infants it was found that the gubernaculum testis arises in a position corresponding to the future spermatic hiatus between the ventromedial borders of the abdominal muscle mass and the lateral border of the rectus. Through this interruption there is first formed a pocket of peritoneum long before the testis is forced into it. Into the scrotal sac, lined with peritoneum, which must be looked upon as an extension of the peritoneal cavity, the testis descends, or passes with swiftness, during stages between 23 and 24 cm. Immediately the muscle plates differentiate behind the escaped gonads by a process of tangential splitting of the single muscle sheet into external and internal layers. The testis is entrapped in the sac by the downward and forward movement of the outer ring and the upward and lateral shift of the inner ring. The fascial layers are then differentiated around the gonad and not pushed along with it from the layers of the belly wall. Thus is the inguinal canal formed by a process of differentiation. Suggested force pushing the gonad through the hole already made and ready for it, is increasing intra-abdominal pressure.

A study of the media of the aorta and the femoral artery of the mouse at different ages. Christianna SMITH, Katherine PIERSON, and Margaret SEITNER, Department of Zoology, Mount Holyoke College.

The aorta and femoral artery of mice from birth to about 700 days were studied in sections impregnated with silver and/or stained in resorcin-fuchsin, orcein, and Mallory's connective tissue stain. During its life history the media increases in width (aorta; average, 29μ , 2 hours through 3 days; average, 46μ , 20 through 713 days; average, 54μ , 337 through 713 days; femoral artery; average, 8μ , 2 hours through 3 days; average, 26μ , 20 through 669 days; average, 31μ , 359 through 669 days). The number of elastic membranes (± 5 , range 4-6) in the aorta is remarkably stable. In both kinds of arteries, the width of single membranes doubles by 20 days and remains fairly constant thereafter. A network of reticular fibers accompanies the elastic lamellae, appearing at first as thin fine lines and later when the membranes have attained their characteristic thickness, as networks on the inner and outer surfaces (inner elastic membrane, mostly on outer surface). A branching and gradual increase of argyrophil fibers among the muscle cells occurs in arteries of mice over 35 days old until in much older animals the wall has a shaggy appearance. A decrease in muscle, an appearance of fine scant fat droplets, a differentiation of white and elastic fibers are found with this multiplication of reticular fibers in arteries of mice over a year old.

Electro-anatomical studies on a tectocerebellar pathway. Ray S. SNIDER, Department of Physiology, The Johns Hopkins University.

By recording evoked electrical changes at the pial surface of visual area of the cerebellum (Snider and Stowell, '44) following weak electrical stimulation of various points on the dorsal surface of the superior colliculus, it has been possible to demonstrate in the cat a tectocerebellar pathway. Maximal responses, surface positive in character are found in the tuber vermis and lobulus simplex. Smaller surface positive responses, as well as occasional surface negative and diphasic ones can be obtained in cerebellar areas immediately surrounding the tuber vermis and lobulus simplex. Response latencies vary from 10 to 16 msec.

The relation between the superior colliculus and cerebellar cortex is such that distinct portions of the former are projected in a definite pattern upon the latter. This projected pattern is largely ipsilateral in character although minor bilateral and contralateral projections do occur. This work affords additional support for the existence of a tectocerebellar pathway in the cat and augments the evidence, first brought forward by Snider and Stowell ('42), that a visual area is present in the cerebellum.

The potential changes were recorded by means of a three stage resistance capacity coupled amplifier and a cathode ray oscillograph by way of a cotton wick pick-up electrode. Sodium pentobarbital anesthesia was used.

On the white pulp lymphatics of the spleen. Theodore SNOOK, Department of Anatomy, Syracuse University.

Current opinion favors the statement that deep lymphatics are lacking in the spleen. However, the examination of sections of guinea pig spleens impregnated for reticulum revealed the presence of an extensive series of anastomosing channels following closely the branches of the white pulp arteries as they radiate from the hilus into the interior. These periarterial vessels were found in all parts of the splenic white pulp strands. Near the hilus their diameter may be as much as 75μ . The finer terminal branches become lost in the meshes of the reticulum.

Adjacent sections stained with hematoxylin and eosin showed that these channels are lined by an endothelium resting upon reticulum, and that they are filled with lymphocytes in some areas and empty in others. Just before piercing the hilus, the larger channels generally form smaller anastomosing ones which empty into mesenteric lymphatics.

It is concluded that the guinea pig spleen contains deep white pulp lymphatics which act as an accessory route for lymphocyte removal. A similar series of lymphatics was also found in the spleens of moles. In 1891, Bannwarth described similar vessels for the shrew. In the horse, white pulp lymphatics leading into trabecular vessels were found, thus corroborating the results of Tomsa (1863), and Kyber (1872).

Volumetric and reconstruction studies of the primate cerebellar nuclei. Othmar SOLNITZKY, Georgetown University Brain Research Institute.

The cerebellar nuclei were studied volumetrically and by wax reconstruction (20 X) in: Galago, Potto, Cebus, Ateles, Cercopithecus, Macaca, Cercocebus, Papio, Pan and Homo. The smallest absolute volumes were found in Galago; the largest, in man. The absolute volume of the dentate was 232.20 cu. mm. in man and only 1.49 in Galago. Between these two extremes, the absolute volume of the dentate in the other forms ranged as follows: Pan, 93; Papio, 54.76; Ateles, 32.3; Cercocebus, 26.8; Macaca, 19.2; Cebus, 12.11; Cercopithecus, 11.9; and Potto, 2.08 cu. mm. On a percentage basis, the study shows that in Galago and Potto the four cerebellar nuclei are approximately of the same volume. As the scale is ascended, there is a marked increase in the percentage of the dentate from 26.38% in Galago to 75.7% in man. The fastigial has a percentage volume smaller than that of the dentate, but rather consistently larger than that of the emboliform and globosal. The lowest percentage volumes of these three nuclei are found in Pan and man, with Ateles occupying an intermediate position.

The reconstructions show that while in lower forms there is variable fusion between the four cerebellar nuclei, nevertheless, even in the lowest form studied it is fairly easy to distinguish between the four nuclei. There is, therefore, no justification for lumping the emboliform and globosal nuclei into a nucleus interpositus.

Volumetric and reconstruction studies of the mammalian lateral geniculate nucleus. Othmar SOLNITZKY, Georgetown University Brain Research Institute.

The lateral geniculate nucleus was studied volumetrically and by wax reconstruction in the following forms, the absolute volume being given in cu. mm. in parentheses: Rodents: Cynomys (1.8), Lepus americanus (5.9), Erethizon (6.2), Lepus callotis (8.7); Carnivores: Mephitis (2.8), Putorius (5.4), Cercopithecus (9.2), Mustela (13), Vulpes (29.3), Canis (30.5), and Lynx r. (46.04); Ungulates: Tayassu (43.5), Ovis (65.8) and Bos (224.8); Subprimates: Lemur (2.8), Potto (3.2) and Galago (4.4); Primates: Cebus (23.3), Macaca (31), Cercopithecus (32.6), Ateles (35.3), Cercocebus (35.7), Papio (54.56), Pan (61.9), Homo 130 mm. fetus (5.63), Homo 180 mm. fetus (6.76), Homo newborn (20.2) and Homo adult (125.2).

The reconstructions show that the shape of the nucleus is characteristic for the various orders, it being easy to distinguish a carnivore lateral geniculate from the ungulate or primate type. In primates it is also possible to identify the individual species by the external form of the lateral geniculate. In rodents, carnivores and ungulates, the form is dominated by the relative size of the segments of the lateral geniculate representing the peripheral retinal quadrants. In subprimates, especially Lemur and Galago, the form of the nucleus is influenced by the appearance of the macular segment. In primates, the models show distinctly the various segments of the nucleus representing the macular, upper and lower peripheral retinal quadrants in accordance with their importance in the visual activity of the respective animal.

Experiments on the development of the posterior neural plate in Amblystoma. Walter R. SPOFFORD, Department of Anatomy, Vanderbilt University. (Introduced by Sam L. CLARK.)

Homotopic grafts of posterior neural plate at Harrison stage 14 between unstained and Nile-blue sulphate stained embryos demonstrate anew that this area forms the myotomes of

the posterior trunk and tail. In the latter region, the meninges, perichordal mesoderm, mesonephros, and fins are entirely or partly from such grafts, while the posterior limb-buds contain graft elements.

Heterotopic grafts to the flank differentiate into muscle, mesonephros, and limb-bud, as well as a "tail" of skin and mesenchyme, while the graft induces an alimentary diverticulum in the host. Normal appearing posterior limb-buds develop in the donor, while the graft furnishes other limb-buds in the host. The materials of the posterior limb-bud may have more than one source.

Heterotopic grafts of prospective posterior neural plate from late gastrulae demonstrate that distinctive mesodermal properties are already present before induction provides for the neural properties of more anterior neural plate regions. Induction of the neural plate may not be responsible for the mesodermal properties of its posterior region.

Grafts of stage 10 prospective ectoderm, replacing the posterior neural plate of stage 14 neurulae, undergo delayed neural tube formation, and later form myotomes flanking the host spinal cord of the posterior trunk and tail. This experiment demonstrates that induction can operate, on competent embryonic material, to produce normal mesodermal structures characteristic of the posterior neural plate. The role of induction in posterior neural plate determination is being studied further.

Some effects of castration and splenectomy on the red blood cells of the golden hamster.

Kathryn F. STEIN and Edith CARRIER, Department of Zoology, Mount Holyoke College.

Castration, whether performed prior to or following maturity, resulted in a red cell count of approximately 6.5, as compared with the normal of 9 million cells per cu. mm. The low level was maintained until other treatment was initiated or counts discontinued, from one to six weeks in different animals. Splenectomy produced a similar decrease in numbers of cells; normal adults after splenectomy dropped to the "castrate level" of 6.5 million, and this level was maintained for at least six weeks. Splenectomy of castrated animals, however, produced no change in count. The picture for castrates was similar to that for splenectomized animals also in that the average size of the cells, the mean corpuscular volume, increased following either type of operation. Daily injections of liver extract or iron citrate for 3 days restored the normal count and decreased the mean corpuscular volume in all animals. Testosterone, injected for a similar period, produced a rise in count and decreased size of cells in castrates only. The splenectomized animals, whether castrated or not, showed no response when tested, like the other injected animals the day following the last injection. It is suggested that the initial effects of castration on the erythrocytes are mediated through the spleen and the splenic function is involved in regulating the average size of the red blood cell, perhaps by affecting iron metabolism.

*The photometric histochemical study of tissues.*¹ Robert E. STOWELL, The Department of Pathology, Washington University and The Barnard Free Skin and Cancer Hospital.

Photometric apparatus has been constructed which is suited for the measurement of amounts of stain or pigment in sections of tissues or blood films. The instrument consists of a stable light source, filters, microscope, photometric cell and amplification and recording apparatus. By employing a stain which is specific for one tissue component, one can compare the relative amounts of numerous substances. The area in which the absorption is to be measured can be visualized through the microscope and the measurements are correlated with the volume of tissue, cytoplasm and nuclei. The ability to examine and compare measurement on different adjacent cells and to relate the results to the cell are important advantages over usual macrochemical methods.

¹ This investigation was aided by grants from the International Cancer Research Foundation and the Jane Coffin Childs Memorial Fund for Medical Research.

This photometric instrument is being employed on studies of desoxyribose and ribose nucleic acids and phosphatase in normal and neoplastic tissues. Other substances which might be measured include bacteria, calcium, carbon, chromatin, collagenous fibers, colored injection masses, cytoplasmic granules, elastic tissue, lipids, glycogen, hematogenous pigments, iron, melanin, melanoblasts, reticulum and silver. The instrument is useful in quantitative studies on tissue staining. The intensity and fading of several stains has been measured. Such apparatus offers a new quantitative approach in a large variety of histochemical problems on normal and pathologic tissues.

Neuromuscular-like fibers of the vocal ligament. Leon H. STRONG, Department of Anatomy, University of Michigan.

Certain slender muscle fascicles, some terminating in single fibers, invade the vocal ligament far medial to the most medial fibers of the main mass of vocalis fibers. They end among fibers of the vocal ligament, in clumps of intertwined fibers or in long spikes. It is suggested that they are a proprioceptive tension apparatus, a modification of a neuromuscular spindle. Their tenuous spiked ends are in a position to respond to small increments of tension in the vocal ligament. These slender isolated fibers can have little pulling strength to alter the forces operating on the glottic edges. Such a tension apparatus in the ligament may well be the sign for relative tenuousness of the ligament in the production of optimum physical conditions at any specific pitch, somewhat in the manner that the tensor tympani operates to alter the tension in the tympanic membrane.

Fluid normally present on the pulmonary respiratory surfaces of terrestrial vertebrates. R. J. TERRY, Department of Anatomy, Washington University.

Observations and experiments during many years have tended increasingly to confirm the discovery of fluid in sufficient amount to constitute a layer on the walls of the pulmonary alveoli of living mammals (cat, dog, rat), pulmonary sinuses of reptiles (turtle, lizard) and of amphibians (frog, salamander). This fluid can be collected in the living by means of capillary tubes. It is the medium in which the vital activities of the macrophages in the mammalian lung have been described. It is a medium in which oxygen is probably dissolved before it passes into the blood and which probably takes carbon dioxide into solution in its passage from the blood into the air spaces of the lung. There is evidence indicating that the lung fluid is derived in part from the blood in the capillary networks of the air spaces. The inspired air of mammals is nearly saturated with water vapor when it enters the lung. It is a fact long established that the mammalian lung can tolerate the intake of relatively large quantities of isotonic fluid and can resorb and eliminate this with astonishing rapidity and without serious damage.

Anatomical restudy of Denonvilliers' fascia. Charles E. TOBIN, Department of Anatomy, The University of Rochester.

Denonvilliers' fascia is a "V-shaped" layer of collagenous tissue, containing bundles of smooth muscle, which extends from the pelvic diaphragm to the pelvic peritoneum in the adult male and female, as observed in histological sections of pelvic organs and dissections of adult pelvis. This fascia intervenes between the areolar-adipose tissue surrounding the rectum and the fibro-muscular tissue on the posterior surface of the pelvic urogenital organs. Laterally Denonvilliers' fascia extends around the sides of, and blends with, the connective tissue of the rectum. Anteriorly in the male, it adheres to: the prostate at the level of the ejaculatory ducts, the apex of the seminal vesicles, and the postero-superior surface of the bladder; in the female, it is sometimes adherent to the posterior wall of the vagina.

This fascia appears to be derived from the connective tissue remaining from the cul-de-sac of peritoneum, which extends to the level of the developing levatores ani muscles in male and female embryos—surrounding the lateral and anterior surfaces of the rectum. With enlargement and change in position of the pelvic viscera, the lumen of the cul-de-sac is obliterated by progressive caudo-cranial fusion and regression of the mesothelial cells. Mesothelial cysts may be found where the fusion was not complete. Mesenchyme surrounding the epithelium and muscular coats of the pelvic viscera appears to form their intrinsic connective-tissue sheaths.

*The sacrococcygeal articulation in American Whites and Negroes.*¹ Mildred TROTTER and Patricia F. LANIER, Department of Anatomy, Washington University.

The incidence of ankylosis of the sacrococcygeal articulation according to age was determined in two hundred ninety-six White males, two hundred thirty-one White females, two hundred fifty-four Negro males and four hundred thirty-six Negro females.² The age range was from 14–101 years. In the Whites more than 50% presented sacra with coccyges fused, whereas the incidence was reduced to 30% among the Negroes. There was no sex difference. The White skeletons averaged 15 years older than the Negroes but, when the data were analyzed for age differences, it became evident that ankylosis of the coccyx to the sacrum, although less common among Negroes, occurred at an earlier age than in Whites.

¹ Aided by a grant from the U. S. Public Health Service.

² Dr. Norman L. Hoerr granted us the privilege of examining the female sacra in the Todd Skeletal Collection at Western Reserve University.

Influence of methylcholanthrene on the thyroid and parathyroids of mice. John H. VAN DYKE, Department of Anatomy, Washington University.

Application of 0.6% methylcholanthrene in benzene to skin of adult mice (New Buffalo) invariably induces marked changes in thyroid and parathyroid parenchyma—prior to development of skin epitheliomata. Following hyperplasia of principle cells, progressive parathyroid hypertrophy produces pronounced cell cords, occasionally follicle-like with mucoid colloid, which penetrate thyroid tissue.

Concomitant with colloid distension of typical peripheral thyroid follicles, which exhibit little evidence of resorption, a centro-median hyperplasia initiates development of bizarre, highly secretory cystoid follicles that occupy much of the thyroid. Cysts have hypertrophied columnar epithelium with long tufts of cilia, most prominent after prolonged carcinogenic application in areas indicative of rapid resorption of aberrant colloid, and possess variable cytoplasmic granular or globules. Differential staining indicates these secretory masses are variable (frequently mucoid), partially or wholly distinct from normal colloid and contain numerous crystalloid platelets.

Evidence suggests cystoid follicles develop after birth from thyroid-like vesicles, derived originally from ultimobranchial tissue, which become released from normal thyroid function; undergoing hyperplasia and metaplasia in response to inactivation of typical parenchyma, caused here by absorption of carcinogen. This atypical secretion, indicative of cyclic phenomena dependent on factors altering thyroid activity, may conceivably be at times harmonious or occasionally incompatible with normal thyroid physiology, possibly with marked effect, and suggests interrelationships with other organs, one of which may be skin. Subsequent publication on experimental manifestations of ultimobranchial tissue will include additional details.

Behavior of ultimobranchial tissue in the thyroid gland of the steer. John H. VAN DYKE, Department of Anatomy, Washington University.

As in sheep ultimobranchial tissue is readily demonstrable in postnatal thyroid glands of cattle. In steer its bulk lies within a prominent vasculostromal hilus, usually attached to para-

thyroid IV, and consists of a compact mass of chromophilic cells arranged as chains of tiny vesicles, without detectable secretion, possessing high columnar epithelium; or "nests" of undifferentiated "clear cells" similar to "macrothyrocytes".

Radiating cell cords, projecting into adjacent active thyroid parenchyma of these castrate cattle, develop aberrant thyroid-like follicles (cystoid) that yield additional vesicles by a process of "budding" or undergo metaplasia to stratified squamous epithelium. This epithelium produces clumps of new, gland-like cells of two kinds which come to lie in adjacent stroma. Certain densely staining cell clusters transform into atypical thyroid-like follicles that secrete acidophilic colloid and appear very hyperplastic. "Clear cells", very numerous in these glands, persist typically as indifferent interfollicular "nests" but occasionally develop into small vesicles lined by clear hypertrophied epithelium that often secrete basophilic colloid showing little evidence of resorption.

Evidence indicates ultimobranchial tissue persists after birth in cattle as relatively dormant tissue in regions remote from thyroid parenchyma. However, intimately associated with active thyroid tissue, it apparently responds by undergoing hyperplasia. Such cells frequently transform into thyroid-like tissue, including atypical parenchyma rich in peculiar cells that occasionally may be responsible for aberrant thyroid secretion.

Mating and pregnancy in the monkey. G. van WAGENEN, Department of Obstetrics and Gynecology, Yale University.

In 1935 controlled breeding of monkeys (*Macaca mulatta*) in the Yale Obstetric Colony was commenced in order to have a self-reproducing group thus attempting some homogeneity and avoiding the repeated introduction of disease. Records of matings which resulted in one hundred and sixty pregnancies are presented. The twenty-four hour period common to the greatest number of these matings which were followed by pregnancy extended from noon of the eleventh day of the menstrual cycle to noon of the twelfth. Young animals were not mated during puberty; multiparous animals were not mated within 3 months after a full term pregnancy even if menstrual cycles did occur; and too, the anovulatory cycles characteristic of this species during summer months were often skipped. Occasionally sterile animals were encountered; but since unfavorable times for conception were for the most part avoided, the result was that over half (56%) of the animals became pregnant after two matings each, including 32% of the monkeys which became pregnant with a single mating.

*Pre-implantation ova of the golden hamster (*Cricetus auratus*).* John H. VENABLE, Department of Anatomy, Emory University.

A series of seventy-three hamster ova up to 96 hours after the termination of a 30-minute copulation period have been collected in sectioned material. Others have been observed at some stages in tubal washings.

Of fifteen ova at 6 hours the typical stage seems to be that of formation of second polar body and in one section a structure resembling a sperm may be seen.

Other data are: twelve ova at 12 hours show two pronuclei; nine ova at 18 hours show two pronuclei; eight ova at 24 hours show either adjacent pronuclei or first cleavage division; eight ova at 36 hours show mostly the two-cell stage; three ova at 48 hours show two or three cells; three ova at 60 hours are all four-cell stage; five ova at 72 hours have eight and nine cells; six ova at 84 hours have from nineteen to twenty-four cells and a blastocoele; while four blastocysts at 96 hours have in the neighborhood of fifty cells each.

Ova of 72 hours are in the upper end of the uterus while at 84 hours they have a blastocoele and are spaced along the uterus lying in antimesometrial crypts. At 96 hours the uterine epithelium has shortened in well-localized regions forming a cup to fit the blastula.

*Injury to paranasal sinuses by simulated blast impacts.*¹ James W. WARD and Sam L. CLARK, Department of Anatomy, Vanderbilt University.

A series of rats and young cats were subjected to water immersion impacts with only the head submerged. Impacts were produced by dropping a weight onto a steel plate in contact with water at one end of a U-tube, the animal being in the water at the other end with both ends of the tube open to atmospheric pressure. Such impacts have been shown to produce effects on animals similar to those of explosives in air or water. Impacts somewhat greater than those which produce fatal pulmonary hemorrhage and perforation of the intestine resulted in disruption of the walls of air-containing sinuses of the head. The immediate manifestations were nose bleed, interference with respiration, and, at times, disturbances of placing reactions and equilibration. Post-mortem examination revealed hemorrhage in some or all of the paranasal sinuses, the middle ear and tympanic bullae. The amount of damage varied with the severity of the impacts, the greatest impacts resulting in fracture of walls of the sinuses. Adjacent to the frontal sinus in some instances rupture of the dura and subcutaneous and intracerebral hemorrhages occurred. Subdural and subpial hemorrhage also occurred following lighter impacts without visible rupture of the meninges. The animal did not lose consciousness. Some of the symptoms appeared to be related to damage to the internal ear and the frontal portion of the cerebrum.

¹ The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Vanderbilt University. Permission to publish this paper has been granted by the Committee on Medical Research, A. N. Richards, Chairman.

Conjoined twins and a consideration of two opposing theories of twinning. L. J. WELLS, Department of Anatomy, University of Minnesota.

The case presented is that of twins (*dicephalus tribrachius tripus*) who were born at the end of the seventh lunar month and who died soon after birth. The hearts were united. The digestive tube-as-a-whole was Y-shaped, being double above Meckel's diverticulum and single below it. The embryonic hepatic cords of each twin had fused to produce conjoined livers. This fusion is an exception to Wilder's general rule concerning the development of cosmobia (twins that are symmetrically united). Regarding the two sets of urinary and genital structures, each set had received its embryonic primordia from both twins. In the right twin, there were no manifestations of situs inversus viscerum that owed their origin to the reversal of such early asymmetries of the embryo as rotation of the stomach to the left or looping of the heart to the right.

The two opposing theories considered are the "budding" theory of Stockard and the "fission" theory of Newman. Contrary to Newman, the occurrence of such anomalies as right aorta in the right twin does not constitute evidence which supports his theory. It is an open question as to whether the left twin can induce the development of situs inversus viscerum in the right twin. At present both theories should be viewed as useful working hypotheses.

Pigmentation of the scrotum as a sensitive indicator for androgen. L. J. WELLS, Department of Anatomy, University of Minnesota.

Having become dissatisfied with the weight of the chick comb as an indicator for the presence or absence of androgen in mammalian adrenals, search for a more sensitive indicator was begun by making additional observations on the deposition of pigment in the scrotum of the striped ground-squirrel (*Citellus*) — a species in which the scrotum, during the breeding season, becomes black.

In each of the twenty-three immature animals having non-pigmented scrota (5 of them castrated) testosterone in 95% ethanol was applied locally by depressing the scrotum with a

wire loop, by dropping the solution into the dimple thus produced and by allowing the alcohol to evaporate before removing the loop. Each scrotum received one application per day for 10 days. Total micrograms of testosterone ranged from 0.63 to 1000. On day 11, the amount of pigment was estimated.

Twenty scrota had become pigmented. Of three scrota receiving a total of 0.63 micrograms each, only one exhibited pigment. Of three receiving 1.25 micrograms (one animal castrated), three showed pigment.

It is concluded that pigmentation of the scrotum of the ground squirrel is an indicator which is sensitive enough to detect 1.25 micrograms of testosterone. This indicator is as sensitive as that involving the beak of the sparrow (Pfeiffer, Hooker and Kirschbaum, '44) but not more sensitive.

Cyclic changes in the mental gland and reproductive system of the male Eurycea bislineata (Green). Charles K. WEICHERT, Department of Zoology, University of Cincinnati.

Weekly collections of adult specimens of the salamander, *Eurycea bislineata*, were made for an entire year near Cincinnati, Ohio. Sections of mental glands, testes and vasa deferentia of representative males, and spermathecae of representative females were studied. *Eurycea* breeds in late March and early April. Spermatozoa have left the testes about a month before the breeding season and the vasa deferentia are distended. At the same time tubules of the hedonic mental gland are filled with secretion. Vasa deferentia and mental gland regress within 2 or 3 weeks after the breeding period and remain degenerate until August. Spermatogenesis begins early in June. Spermatids first appear in late July and early August and at the same time the mental gland begins to develop. Growth of the vasa deferentia follows shortly. At the end of September spermatogenesis is complete and spermatozoa enter the vasa deferentia. Secretion appears in the tubules of the mental gland late in October when an "autumnal mating" may take place and spermatozoa first appear in the spermathecae of the females. Animals are capable of reproducing almost five months before the actual breeding period. Changes in secondary sex characters, presumably brought about by action of male hormone, appear concomitantly with changes in the testes associated with the later stages of spermatogenesis.

The variation of blood alcohol levels following the administration of alcohol in normal cats and in cats with hypothalamic lesions. M. D. WHEATLEY, Department of Anatomy, University of South Dakota. (Introduced by W. R. INGRAM.)

Bilateral hypothalamic lesions were placed in the brains of twelve selected friendly cats. These were allowed to recover before commencing the alcohol experiments. Unoperated control cats consisted of eight tame animals and four wild ones that had never been tamed. All were given the same relative amount of alcohol intravenously. Blood was drawn from superficial veins at regular intervals and per cent of alcohol determined. Intensity of symptoms of intoxication were observed and correlated with blood alcohol percentages.

Following adequate recovery periods the animals were fed alcohol by stomach tube. Amounts given were proportionate to body weight. Alcohol levels and symptoms were noted as before. At the conclusion of this experiment the operated cats and two each of tame and wild normal animals were sacrificed. Their brains were examined histologically.

Results: Three operated cats became malevolent. These had lesions destroying the region of the ventromedial hypothalamic nuclei. The brains of the others showed either no pathology or destruction of other hypothalamic structures. Following alcohol feeding by stomach tube, the percentage of alcohol in the blood of these three greatly exceeded that attained in the other animals. No such differences were noted after intravenous alcohol injections. The interpretation offered is that alcohol is absorbed at an increased rate in cats with destruction of the region of the ventromedial hypothalamic nuclei.

A description of an accessory peritoneal sac in a human subject. J. L. WIERDA, Department of Anatomy, University of Pennsylvania.

A peritoneal sac containing the jejunum, ileum and transverse colon was found in the greater peritoneal sac of a human cadaver. The abdominal cavity was normal except for the presence of the sac and the concomitant absence of the inferior recess of the omental bursa. The sac was globular in form, and pendulous, extended from pancreas to pelvis, and occupied the area between the ascending and descending colon. The great omentum hung in front of the sac, and the posterior lamellae of the omentum were separated from the transverse colon and transverse mesocolon by the sac.

The first impression received from this specimen is that this is another case of paraduodenal hernia. That interpretation is, however, untenable in view of the normal position and attachment of the duodenum, and other viscera, and the fact that the transverse colon with its mesocolon lies in the sac with the ileum and jejunum. The condition found here is believed more likely to have resulted from an adhesion between the parts of the digestive tube within the sac and the embryonic sac of peritoneum which protrudes into the umbilical cord. Such an origin was first postulated by Papez in 1932. Direct observations upon developing peritoneal sacs such as was found in this specimen have not been made, consequently their source (or cause) is still a matter of speculation.

Microscopic studies of living grafts from the adrenal cortex of rabbits. Roy G. WILLIAMS, Department of Anatomy, University of Pennsylvania.

Using the transparent chamber method, autogenous grafts of adrenal cortex were studied under an oil immersion lens for 8 months.

In grafts of glomerulosa cells alone blood vessels were stimulated to grow and formed close-meshed permanent plexuses in them.

Grafts of fasciculata cells produced scarcely any vascular response.

An abnormal position in a vascular gradient had no apparent effect on glomerulosa cells.

There was evidence that capillaries in glomerulosa grafts were more permeable than elsewhere.

Glomerulosa cells persisted for the entire period of 8 months. They were characterized by their small size and granular cytoplasm. They slowly changed from a granular to an agranular state and back again. The complete cycle of changes required about 3 months. The capsule had no observed effect on the survival of glomerulosa grafts nor upon the number of cells therein.

Fasciculata cells were large. Their nuclei were obscured by refractile droplets. They underwent changes which were probably secretory. They slowly but steadily diminished in number.

No transitions between glomerulosa and fasciculata cells were seen nor were any mitoses observed.

Mammary development in the newborn human. W. Lane WILLIAMS and Chester A. STEWART, Departments of Anatomy and Pediatrics, Louisiana State University; and Charity Hospital, New Orleans, Louisiana.

The material included twenty full-term foetuses. In these the mammary parenchyma consisted of a well developed system of large ducts whose distribution suggested the definitive lobar structure of the breast. No true intralobular ducts or alveoli were present in the foetal glands if the size and structure of these elements in the adult breast are used as criteria for identification. However, these tubular structures of the late foetal gland were lined by cells whose similarity to the epithelium of intralobular ducts and alveoli in the adult parturient or lactating gland was much more pronounced than their resemblance to the epithelium of the primary duct system of the adult breast. The cells lining the ducts were vacuolated and granular; and

showed distortion and accumulations of basophilic material at their luminal borders. No secretion was observed other than this basophilic material. The stroma was well differentiated. It was dense and fibrous in contrast to the adjacent and underlying loose areolar tissue.

At term the total amount of breast development varied considerably. The diameters of these glands ranged from 5 to 21 mm. These differences in size of the mammary glands bore no relationship to the weight or sex of the foetus. The largest glands in the series were from a male foetus. The two smallest were from luetic foetuses.

Cornification of urethral epithelium in young male rats following injection of estrogen. James G. WILSON, Department of Anatomy, University of Rochester.

A sequence of changes is initiated in the epithelia of the urethra and associated glands by six injections of 0.1 mg. of estradiol dipropionate during the first 2 weeks of life. These eventually culminate in extensive replacement of the characteristic epithelia by one of stratified squamous type exhibiting cornification and desquamation of the superficial cells. Beginning at the seventh day, after three injections, marked stratification and hypertrophy (60% overall increase in thickness) are observed in epithelia throughout and particularly in the ejaculatory ducts. Successive injections induce further hypertrophy and the appearance of typically squamous cells on the surface. True cornification, evidenced by formation of keratohyalin granules and subsequent disappearance of the nuclei, is first seen as isolated patches in the ejaculatory ducts at 10 days, after four injections. At 15 days, after the sixth and last injection, cornification together with extensive desquamation are seen throughout the ejaculatory ducts and prostatic utricle as well. This metaplasia occurs in the main ducts of the bulbourethral glands and on the colliculus seminalis by the eighteenth day. It appears in the dorsal prostatic ducts, ducts of the coagulating glands and on the dorsal wall of the urethra proper around the colliculus and openings of the bulbourethral glands, by the twenty-second day. Portions or all of the remaining epithelium are subsequently involved by gradual spreading from these foci.

Depletion of the cervical sympathetic trunks and ganglia following removal of neural crest in the chick. C. L. YNTEMA and W. S. HAMMOND, Department of Anatomy, Cornell University Medical College.

The cervical sympathetic trunks in the chick consist of (1) a postcarotid trunk with several small ganglia and (2) a paravertebral chain with its ganglia arranged segmentally in relation to all the cervical nerves except the first two. These trunks connect with each other and with the superior cervical ganglion. The paravertebral chain continues below into the thorax. Preganglionic fibers for the cervical region arise from the upper thoracic nerves, and probably from the last cervical nerve (Terni).

Neural crest was removed from the occipital and cervical regions of chick embryos at stages ranging from nine to nineteen somites. Ten animals preserved 5 or 6 days after the operation are available for study.

Appropriate extirpation of neural crest results in absence or marked reduction of (1) dorsal root ganglia, (2) paravertebral trunk and ganglia, (3) post-carotid trunk and ganglia, and (4) superior cervical ganglion. Removal of neural crest for a width of about eight somites is necessary to produce a gap in the chain of paravertebral ganglia due to post-operative migration of components into the region of extirpation.

The experiments indicate that the postganglionic sympathetic neurons arise from neural crest cells. Preganglionic fibers from the upper thoracic cord may ascend for a few segments in the neck when the paravertebral ganglia are absent. Moreover, small sympathetic ganglia may differentiate in absence of the preganglionic fibers.

Changes in epidermal nuclear size induced by methylcholanthrene application. Dorothy M. ZIEGLER, Department of Anatomy, Washington University School of Medicine and Barnard Free Skin and Cancer Hospital. (Introduced by E. V. COWDRY.)

A technique has been developed whereby it is possible cleanly to separate nuclei from other components of epidermis (Anat. Rec., '45 in press). To be able easily to examine large numbers of whole nuclei supplements and extend the study of epidermal nuclei in stained sections. This method has been used as a means of investigating alterations in nuclear size in the course of epidermal carcinogenesis in mice produced by applications of 0.6% methylcholanthrene in benzene to the skin of the back. Increases in nuclear size have been observed which are maintained in the period of precancerous epidermal equilibrium, whereas the increase in nuclear size in control epidermises treated only with benzene has been found to be of short duration.

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1922. H. H. Wilder	Bennet M. Allen	H. V. Wilson—5 years
1923. M. F. Guyer	Robert A. Budington	M. M. Metcalf—5 years
1924. R. G. Harrison	R. K. Nabours	George Lefevre—5 years
1925. C. R. Stockard	C. R. Moore	C. M. Child—5 years
1926. S. O. Mast	W. C. Allee	G. A. Drew—5 years
1927. S. J. Holmes	Robert Chambers, Jr.	C. A. Kofoid—5 years
		H. H. Wilder—5 years
		J. H. Gerould—1 year
1928. Caswell Grave	M. H. Jacobs	M. F. Guyer—5 years
1929. C. B. Davenport	Fernandus Payne	R. G. Harrison—5 years
1930. H. V. Neal	E. E. Just	C. R. Stockard—5 years
1931. Fernandus Payne	D. E. Minnich	S. O. Mast—5 years
1932. W. C. Curtis	L. V. Heilbrunn	S. J. Holmes—5 years
1933. Charles Zeleny	J. H. Bodine	Caswell Grave—5 years
1934. A. H. Sturtevant	H. W. Rand	C. B. Davenport—4 years
1935. R. W. Hegner	Sewall Wright	H. V. Neal—5 years
1936. W. C. Allee	C. W. Metz	Fernandus Payne—5 years
1937. F. L. Hisaw	Helen D. King	W. C. Curtis—5 years
1938. M. H. Jacobs	T. S. Painter	Charles Zeleny—5 years
1939. J. T. Patterson	H. B. Goodrich	A. H. Sturtevant—5 years
1940. W. R. Coe	D. H. Wenrich	Robert W. Hegner—5 years
1941. R. E. Coker	J. P. Visscher	W. C. Allee—5 years
1942. L. L. Woodruff	C. G. Hartman	F. L. Hisaw—5 years
1943. T. S. Painter	L. H. Snyder	M. H. Jacobs—5 years
1944. Sewall Wright	H. W. Stunkard	J. T. Patterson—5 years

Secretary-Treasurer

1914-1918. Caswell Grave

Secretary

1921-1924. W. C. Allee
 1925-1928. D. E. Minnich
 1928-1929. L. B. Arey
 1929-1930. D. E. Minnich
 1930-1933. W. H. Cole
 1933-1936. H. B. Goodrich
 1936-1939. E. G. Butler

1918-1921. W. C. Allee

Treasurer

1922. D. H. Tennent
 1923-1924. R. H. Bowen
 1925-1930. L. B. Arey
 1930-1933. A. B. Dawson
 1933-1935. B. H. Willier
 1935-1938. W. N. Hess
 1938-1941. T. C. Nelson
 1941-1944. H. W. Beams

Representatives in the Division of Biology and Agriculture, National Research Council

F. R. Lillie 1919-1923	J. T. Patterson 1924-1927	L. C. Dunn 1931-1932
G. H. Parker 1919-1922	L. L. Woodruff 1925-1928	J. H. Bodine 1932-1935
M. F. Guyer 1919-1921	E. G. Conklin 1926-1929	L. V. Heilbrunn 1935-1938
William Patten 1921-1924	G. H. Parker 1926-1929	Laurence Irving 1938-1941
H. S. Jennings 1922-1925	H. S. Jennings 1929-1931	D. E. Minnich 1941-1944
E. G. Conklin 1923-1926		

Associate Editors of the Journal of Morphology

1921.	Gary N. Calkins	J. S. Kingsley	William Patten
1921-1922.	E. G. Conklin	M. F. Guyer	W. M. Wheeler
1921-1923.	C. A. Kofoid	F. R. Lillie	J. T. Patterson
1922-1924.	G. A. Drew	H. V. Neal	L. L. Woodruff
1923-1925.	Caswell Grave	D. H. Tennent	H. V. Wilson
1924-1926.	Helén Dean King	S. O. Mast	A. A. Schaeffer
1925-1927.	R. W. Hegner	Fernandus Payne	H. B. Ward
1926-1928.	L. J. Cole	J. H. Gerould	M. H. Jacobs
1927-1929.	W. C. Curtis	J. Percy Moore	A. F. Shull
1928-1930.	Edgar Allen	G. A. Baitzell	R. E. Coker
1929-1931.	S. R. Detwiler	R. S. Lillie	H. J. Muller
1930-1932.	W. R. Coe	E. N. Harvey	H. E. Jordan
1931-1933.	L. V. Heilbrunn	S. O. Mast	G. K. Noble
1932-1934.	D. E. Minnich	B. H. Willier	L. L. Woodruff
1933-1935.	L. R. Cleveland	F. L. Hisaw	Franz Schrader
1934-1936.	Charles Zeleny	J. F. Daniel	J. S. Nicholas
1935-1937.	D. H. Tennent	L. C. Dunn	C. G. Hartman
1936-1938.	Sally Hughes-Schrader	E. E. Just	D. H. Wenrich
1937-1939.	Leigh Hoadley	W. A. Kepner	J. Percy Moore
1938-1940.	J. H. Bodine	N. E. McIndoo	H. H. Plough
1939-1941.	J. E. Kindred	H. W. Rand	S. A. Matthews
1940-1942.	A. M. Banta	V. Hamburger	C. W. Metz
1941-1943.	E. G. Butler	W. N. Hess	W. A. Kepner
1942-1944.	L. H. Hyman	A. C. Kinsey	H. W. Rand

LIST OF PLACES OF MEETING

AMERICAN MORPHOLOGICAL SOCIETY

1890—Boston	1894—Baltimore	1899—New Haven
1891—Philadelphia	1895—Philadelphia	1900—Baltimore
1892—Princeton	1896—Boston	1901—Chicago
1893—New Haven	1897—Ithaca	1902—Washington
	1898—New York	

CENTRAL NATURALISTS

1899—Chicago	1900—Chicago
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SOCIETY OF AMERICAN ZOOLOGISTS

1901—Chicago	1902—Washington
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AMERICAN SOCIETY OF ZOOLOGISTS

EASTERN BRANCH	JOINT MEETINGS	CENTRAL BRANCH
1903—Philadelphia	1905—Ann Arbor	1903—St. Louis
1904—Philadelphia	1908—Baltimore	1905—(Mch.) Chicago
1906—New York	1911—Princeton	1907—(Mch.) Madison
1907—New Haven	1912—Cleveland	1907—Chicago
1909—Boston	1913—Philadelphia	1910—(Apr.) Iowa City
1910—Ithaca		1910—Minneapolis
		1912—(Apr.) Urbana

MEETING PLACES

1914—Philadelphia	1925—New Haven	1936—Atlantic City
1915—Columbus	1926—Philadelphia	1937—Indianapolis
1916—New York	1927—Nashville	1938—Richmond
1917—Minneapolis	1928—New York	1939—Columbus
1918—Baltimore	1929—Des Moines	1940—Philadelphia
1919—St. Louis	1930—Cleveland	1941—Dallas
1920—Chicago	1931—New Orleans	1942—New York (cancelled)
1921—Toronto	1932—Atlantic City	1943—No meeting held
1922—Boston	1933—Boston	1944—Cleveland (Sept.)
1923—Cincinnati	1934—Pittsburgh	
1924—Washington	1935—Princeton	

AMERICAN SOCIETY OF ZOOLOGISTS

CONSTITUTION

ARTICLE I

NAME AND OBJECT

Section 1. The Society shall be called the "American Society of Zoologists."

Sec. 2. The object of the Society shall be the association of workers in the field of zoology for the presentation and discussion of new or important facts and problems in that science and for the adoption of such measures as shall tend to the advancement of zoological science.

ARTICLE II

MEMBERSHIP

Section 1. The membership of the Society shall consist of two classes:

a. Associate membership open to all actively engaged in the field of zoology who have had training in zoology equivalent to that required for the doctorate degree.

b. Active membership open to those who hold the doctor's degree in zoology or who have done work equivalent thereto, and who, in addition to the usual requirements for this degree, have published the results of substantial zoological research.

Sec. 2. Election to membership in the Society shall be upon recommendation of the Executive Committee.

Sec. 3. Associate members shall not hold office or vote, but may present papers before the Society without introduction. Associate members shall receive all literature issued by the Society, including the proceedings of the Society, and shall have the same privileges as active members in journal subscriptions.

Sec. 4. Associate members may be elected to active membership in the usual way when the research requirements of active membership have been met.

ARTICLE III

OFFICERS

Section 1. The officers of the Society shall be a President, a Vice-President, a Secretary, a Treasurer, and the members at large of the Executive Committee.

Sec. 2. The Executive Committee shall consist of the President, the Vice-President the Secretary, the Treasurer, and five members elected from the Society at large. Of these five members, one shall be elected each year to serve five years. If any member at large shall be elected to any other office, a member at large shall be elected at once to serve the remainder of his term.

Sec. 3. These officers shall be elected by ballot at the annual meeting of the Society and their official terms shall commence with the close of the annual meeting, except that the Secretary and the Treasurer shall be elected triennially and shall serve for three years.

Sec. 4. The officers named in Section 1 shall discharge the duties usually assigned to their respective offices. (See by-laws.)

Sec. 5. Vacancies in the board of officers, occurring from any cause, may be filled by election by ballot at any meeting of the Society. A vacancy in either the Secretaryship or the Treasurer-ship occurring in the interval of the meetings of the Society may be filled, until the next annual meeting, by appointment by the Executive Committee.

Sec. 6. At the annual meeting the President shall name a nominating committee consisting of three active members. It shall be the duty of this committee to nominate officers of the Society, including the permanent representatives which the Society is asked to name to various boards and councils. This committee shall make its nominations to the Secretary at least four months before the next annual meeting. Additional nominations for any office may be made in writing to the Secretary by any five members at any time previous to balloting.

ARTICLE IV

MEETINGS OF THE SOCIETY

Sec. 1. Unless previously determined by the Society, the time and place of the annual meeting shall be determined by the Executive Committee. Special meetings may be called and arranged for by the Executive Committee. Notices of such meetings shall be mailed to all members of the Society at least two weeks before the date set for the meeting.

Sec. 2. Sections of the Society may be organized in any locality by not less than ten members, for the purpose of holding meetings for the presentation of scientific papers. Such sections shall have the right to elect their own officers and also associate members; provided, however, that associate membership in any section shall not confer membership in the Society.

ARTICLE V

QUORUM

Twenty-five members shall constitute a quorum of the Society and four a quorum of the Executive Committee.

ARTICLE VI

CHANGES IN THE CONSTITUTION

Amendments to this Constitution may be adopted at any meeting of the Society upon approval of two-thirds of the members voting, subject to the following conditions:

a. The proposed amendment must be in writing and signed by at least five members of the Society.

b. This signed proposal must be in the hands of the Secretary at least one month before the meeting of the Society at which it is to be considered.

c. The Secretary shall mail copies of the proposed amendment to the members of the Society at least two weeks before the meeting.

d. Members unable to attend may submit their votes in writing to the Secretary.

BY-LAWS

ARTICLE I

DUES

Section 1. The annual dues for active and associate members, unless remitted or changed by the vote of the Society, shall be two dollars.

Any member in good standing, having paid annual dues to the Society for not less than twenty-five years, who shall change his professional status, may apply to the Executive Committee for the remission of further dues. Applicants approved by the Executive Committee shall be exempt from further payment of dues, but such members shall be entitled to all the privileges of membership formerly enjoyed.

Sec. 2. Any member in arrears of dues for two years should be dropped by the Executive Committee. Upon payment of arrearage he shall be reinstated.

ARTICLE II

PRESIDENT

Section 1. The President shall preside at scientific sessions and at the business meetings.

Sec. 2. He shall also appoint the committees prescribed by the constitution and by-laws.

ARTICLE III

VICE-PRESIDENT

Section 1. The Vice-President shall preside at sessions designated by the President.

Sec. 2. He shall also assume the duties of the President in the latter's absence.

ARTICLE IV

SECRETARY

Section 1. The Secretary shall keep the records of the Society.

Sec. 2. He shall be responsible for all arrangements for the meetings, including the appointment of local committees.

Sec. 3. Whenever the proper officers of a number of related societies shall have a conference covering matters of mutual interest to the several societies, he shall act as the delegate or representative of this Society.

Sec. 4. He shall make such purchases and employ such assistance as will, in his judgment, expedite the business of the Society, and

Sec. 5. He shall be reimbursed out of the funds of the Society for expenses incurred in attending meetings of the Society.

ARTICLE V

TREASURER

Section 1. The Treasurer shall be in charge of the funds of the Society.

Sec. 2. At the annual business meeting of the Society he shall present a statement to date of the funds of the Society.

Sec. 3. He shall make such purchases and employ such assistance as will, in his judgment, expedite the business of the Society.

ARTICLE VI

AUDITING COMMITTEE

The President shall annually appoint an auditing committee of two, who shall audit and report upon the financial record and statement of the Treasurer at the meeting for which they were appointed.

ARTICLE VII

PROGRAM RULES

In matters relating to programs for annual meetings, the following rules shall be observed:

Section 1. Titles and abstracts of papers to be presented by any method at the annual meeting must be sent to the Secretary in duplicate before the final date set by him. The length, form, and arrangement of the abstracts must comply with the requests of the Secretary in order to insure prompt publication by The Wistar Institute. The titles and abstracts of papers which do not conform to such requests or papers which are received late may be presented by title only.

Sec. 2. Titles shall be listed in groups according to subject matter, the groups to be determined by the Secretary.

Sec. 3. Whenever conditions require, the Secretary shall schedule two or more groups for the same hour and arrange the program to bring together papers on subjects of more general interest for meetings of the whole Society.

Sec. 4. Each member may have not more than fifteen minutes of the time of the Society at the annual meeting. This time may be used by him to present one or more papers personally or to introduce papers of non-members.

Sec. 5. All papers not read when called for as listed shall be placed at the end of the group list, and if not read when called for the second time, shall be read by title only.

Sec. 6. The titles of "introduced" papers may be listed in the groups after the titles of papers to be read by members.

PROCEEDINGS OF THE FORTY-FIRST ANNUAL MEETING OF THE AMERICAN SOCIETY OF ZOOLOGISTS

WESTERN RESERVE UNIVERSITY

CLEVELAND, OHIO

SEPTEMBER 12, 13, 14, 1944

PROGRAM

The American Society of Zoologists again held a meeting after cancelling its regular annual meetings for the past 2 years because of transportation and other difficulties arising as a result of the war. The location and time of the meeting were arranged with a view to avoiding congested, war-activities areas, as well as not to aggravate transportation difficulties. The meeting was held in conjunction with Section F of the American Association for the Advancement of Science and in association with several other biological societies. All meetings were held on the campus of Western Reserve University.

The Cleveland Meeting, though not as large as the annual meetings of recent years, was nevertheless well attended and it was the general opinion among those in attendance that it was unusually successful in view of prevailing conditions. The total number of papers on the program scheduled to be presented in person was 84 of which number 12 were presented by demonstration. There were 57 papers included in the program as "read by title". According to reports from the presiding officers of the various sessions, 9 papers were omitted. In all, therefore, 75 papers were actually presented at the sessions of the Society in Cleveland. Included in the foregoing figures are papers presented in the various symposia sponsored by the Society.

The attendance at all sessions of the Society was good and, while no record of actual attendance was available, indications were that the number of Zoologists assembled in Cleveland compared favorably with those assembled at meetings of the Society 8 to 10 years ago.

The Biologists' Smoker was held on the evening of the first day of the meeting, Tuesday, September 12th, in the Grand Ballroom of the Hotel Statler. The attendance was very good. Due to prevailing restrictions refreshments were omitted.

The Annual Dinner of the American Society of Zoologists was held on Wednesday evening, September 13th, in the Euclid Ballroom of the Hotel Statler with 128 persons in attendance. An address on "What is Germ Plasm?" was given by Dr. George T. Hargitt, Vice-President of the American Association for the Advancement of Science and Chairman of Section F.

BUSINESS MEETING

The forty-first annual business meeting opened at 12:30 P.M., September 13th, President Sewall Wright presiding.

The following business was transacted:

1. *The minutes of last year's business.* The minutes of last year's business, which in the absence of the annual meeting was conducted by the Executive Committee as authorized by Society Referendum, were published in the June 1944 supplement of *The Anatomical Record* and distributed to all members of the Society.

It was unanimously voted to approve the minutes as printed.

2. *Memorial resolutions.* The Secretary reported that during the past year the Society had suffered the loss by death of 9 active members. These were Charles Benedict Davenport, Simon Henry Gage, Caswell Grave, Chancey Juday, Frank Eugene Lutz, Ronald F. MacLennan, William Emerson Ritter, Charles P. Sigerfoos, and Colin Campbell Stewart. The following resolutions were prepared.

CHARLES BENEDICT DAVENPORT

In the death of Charles B. Davenport, February 18, 1944, the American Society of Zoologists and science in general suffered the loss of an energetic and distinguished leader. His nearly 78 years of life were filled with many and diverse intellectual activities in some of which he was a pioneer, or, through his ability to stimulate and work with others, was a potent directive force. Among his activities were early work in the field of experimental zoology, in the taxonomy of the Bryozoa, and in the then new field of biometrics in which he published the first text book. These activities were followed by studies on inheritance in canaries and poultry and later some of the early studies on inheritance of human physical and mental characteristics. Still later his interest was focussed upon analysis of human growth and development which studies he continued until the time of his death.

After serving as Assistant or Associate Professor of zoology at The University of Chicago and Harvard University, he was in 1904 selected by the newly founded Carnegie Institution of Washington to establish and direct its Station for Experimental Evolution (later to become the Department of Genetics of the Carnegie Institution). Under his direction and in no small part because of his own contributions this laboratory became outstanding in the field of genetics and certain fields of experimental biology. In 1910 Dr. Davenport was instrumental in establishing the Eugenics Record Office which he directed until his retirement from administrative duties in 1934. He had earlier (1898) become the chief sponsor for the Biological Laboratory at Cold Spring Harbor and was its Director for 25 years. He was a member and official of the National Academy of Sciences and of many other national and international scientific organizations.

Of perhaps equal importance to his development and administration of different institutions (details of administration often annoyed him) were his own contributions to biological science and his interest in and encouragement of other workers whether humble or conspicuous or whether or not within the institutions which he directed. He was an individualist and expected others to be individualists, frankly lauding or criticising their studies, offering pertinent suggestions, and providing such material assistance as he could — but always respecting the individual's freedom of activity. His most important contributions perhaps were his two volume "Experimental Morphology" (1897); his early book on "Statistical Methods" (1899); his contributions to and interpretations of the various genetical studies completed at the Carnegie laboratory which he directed; his late work on human growth and development; and his contributions on human genetics including the establishment of a long-time project for continuing and expanding such studies. This project, embodied in the Eugenics Record Office, is now unfortunately dormant.

Always modest, often to the point of embarrassment, he nevertheless met many workers in many fields and these associations widely extended his stimulating influence.

Always very broad in his interests, his death, while he was still exceedingly vigorous, was apparently brought about by his unduly exposing himself in foul weather in the preparation of a whale's skull for the Whaling Museum which he had established at Cold Spring Harbor.

He is remembered by the American Society of Zoologists as twice its president (1907, 1929) and as a kindly discriminating leader in the furtherance of zoological progress.

A. M. BANTA

SIMON HENRY GAGE

Simon Henry Gage, Professor of Histology and Embryology Emeritus in Cornell University, died at his home in Interlaken, New York, on October 20, 1944. He was born at Crumhorn Lake, Otsego County, New York, on May 20, 1851. His association of 71 years with Cornell University began in the fall of 1873, when he matriculated there as a freshman. His enthusiastic interest in biology immediately attracted the attention of Professor Burt Green Wilder, whom he assisted throughout his undergraduate years. Upon receiving the degree of B.S. in 1877, he was appointed Instructor in Microscopy and Practical Physiology. His subsequent titles were as follows: Assistant Professor of Physiology and Lecturer in Microscopical Technology, 1881; Associate Professor (as above), 1889; Associate Professor of Anatomy, Histology and Embryology, 1895; Professor of Microscopy, Histology and Embryology, 1896; Professor of Histology and Embryology, 1902.

In 1896 he organized in the newly established New York State Veterinary College an independent department of histology and embryology, which was transferred in 1902 to Stimson Hall, then the new home of the Ithaca division of the Cornell University Medical College.

He retired from teaching in 1908 on a pension provided by the Carnegie Foundation for the Advancement of Teaching; but never did he lay aside his interest in research, which he prosecuted with vigor and enthusiasm until his last illness. His final visit to his laboratory was made only 10 days before his death.

On the occasion of his sixty-fifth birthday, in 1916, there was established a fund in support of the Simon Henry Gage Fellowship in Animal Biology. By his ninetieth birthday this had reached the sum of \$10,000, and the first fellow was then appointed.

In 1921-22 he served as a Trustee of Cornell. From 1923-40 he was Librarian of the Van Cleef Memorial Library, now the library of Cornell's department of zoology.

In 1893 Professors Gage and Comstock established the Comstock Publishing Company, which, through the bequest of Comstock and the gift of Gage, became the property of Cornell in 1931, and at that time Professor Gage became President of the company, an office he held until his death. The profits of this enterprise continue to be one of the major sources of the support of Cornell's thriving University Press.

Professor Gage was a prolific contributor to the journals in his field, and the author of several books. His most widely known work, "The Microscope" was first published in 1881, and became probably the most widely used American text on the subject. The seventeenth edition appeared on his ninetieth birthday, in 1941. He was co-author with B. G. Wilder of "Anatomical Technology," 1882; with B. F. Kingsbury of "Vertebrate Histology," 1899; and with Henry Phelps Gage of "Optic Projection," 1914. With John Henry Comstock he edited in 1893 "The Wilder Quarter-Century Book," said to be the first American collection of researches published in honor of a university teacher. Shortly before his death he finished a history of the Comstock Publishing Company, and he leaves the nearly completed manuscript of a history of microscopy in America, a work which it is hoped will be edited for publication by his wife, Clara Starrett Gage, and his son, Henry Phelps Gage.

Professor Gage was long a member of the American Society of Zoologists. He became in 1888 one of the original members of the American Association of Anatomists, and was one of the original board of editors of *The American Journal of Anatomy*, which he assisted in establishing by obtaining from Cornell a subvention toward its support. His seventy-fifth birthday was marked by a dinner given in his honor by the American Association of Anatomists at New Haven in 1926. In 1931, his eightieth birthday was observed by a dinner given by the Advisory Board of The Wistar Institute of Anatomy and Biology, of which he had been a member since the organization of the Board in 1905; and on this occasion he was presented with a copy of volume 48 of *The American Journal of Anatomy*, which was dedicated to him.

He was also a Fellow of the American Association for the Advancement of Science, and twice presided over the meetings of its Zoological Section; a member of the New York State Science Teachers Association (President, 1896), American Microscopical Society (President, 1895-96, 1906), American Society of Naturalists, Royal Society of Arts, Academy of Natural Sciences of Philadelphia, American Fisheries Society, Optical Society of America, and The National Association for the Prevention of Tuberculosis.

While Professor Gage was widely known and respected, only those privileged to work near and with him can appreciate fully the true qualities of the man. He was a distinguished teacher, his whole life a lesson; for in his life and in his work he exemplified the finest traditions of the profession. His influence was widespread, profound, and beneficent. To his laboratory his old students, his associates, and his colleagues in other institutions came constantly for assistance and, above all, for inspiration. His sincere and youthful enthusiasm, his fresh and forward-looking point of view, his fine sense of humor, his hearty, infectious laugh, and his kindly interest in men and their problems struck a responsive chord in all with whom he came in contact. His many friends, the university he loved so well and served so long and devotedly, and American biology are the richer for his life, the poorer for his passing. But, as with all great teachers, his influence will continue to be felt for generations.

HOWARD B. ADELMANN

CASWELL GRAVE

The chief statistical facts of the life of Caswell Grave (January 24, 1870-January 8, 1944) can be briefly recorded; the impact of his life upon students, colleagues, and friends is a longer and more important story, which can only be touched upon within this space.

Caswell Grave spent his early years on a farm near Richmond, Indiana, the son of members of the Society of Friends. This early wholesome environment, which continued on through his college days at Earlham College, influenced all that he said and did throughout his life. The other greatest influence on his thinking, in the opinion of one of his colleagues, was Professor W. K. Brooks, of The Johns Hopkins University, where Dr. Grave was student and professor for a period of 24 years (1895-1919). Until the end of his life, Brooks' FOUNDATION OF ZOOLOGY was his constant companion, and each generation of his graduate students had the privilege of reading and discussing this classic in seminars, under Dr. Grave's guidance. This was a liberal education in itself, not only for his graduate students, but for the members of

his staff, of whom the writer was one. For several years prior to the erection of the new laboratory at Washington University, where he had become Chairman of the Department of Zoology in 1919, these weekly seminars were held in his home and no student or colleague will ever forget those memorable evenings. These seminars were devoted largely to a discussion of the philosophical aspects of biology. In them the students learned respect for the complexity of organisms and cells. To the young enthusiasts for the application of physical and chemical methods this provided a salutary warning that there is need for the organismic as well as the analytical approach to biology. This probably was his greatest achievement in the training of graduate students: that is, the alternation of enthusiastic encouragement of the most modern physical and chemical type of analytical research, with a cautious restraint, begotten of years of close personal experience with "that marvelous stuff" (protoplasm), which ever kept reminding that the co-ordinated functioning of the whole must never be forgotten in detailed investigations of the parts. The good music and simple but well-chosen refreshments, served by a most gracious host and hostess, which followed these "home seminars", made them but the more memorable.

Dr. Grave had what it takes to make a great teacher. And this was no less evident in his undergraduate than in his graduate teaching. Many remember the stimulating manner in which he introduced them to elementary zoology. He had a singular knack of treating even beginning students as co-workers, thus encouraging them to think for themselves and to try to be worthy of such unexpected distinction. And for both colleagues and students his office door was seldom closed; all learned early that not only professional matters but also personal problems could be taken there.

After his retirement in 1939, Dr. Grave divided each year between Woods Hole and his new home in Winter Park, Florida. His satisfaction over the results of his most recent work on the mechanism of metamorphosis of ascidian tadpoles was freely expressed, and he was looking forward to completing his paper describing these experiments, during the coming winter. While this was not to be, fortunately Professor S. O. Mast, who had long been interested in Dr. Grave's work with ascidians and had followed his latest experiments in detail, was able to prepare the paper for publication. This work Professor Mast has described as a comprehensive series of wisely planned and meticulously executed studies concerning the structure, development and interrelationship of ascidians, and he asserts that the results obtained are profound in significance, especially those concerning the factors involved in the metamorphosis of the tadpoles.

About two months before his death, Dr. and Mrs. Grave were guests in the writer's home in New York. During these last evenings which Caswell Grave and the writer spent together, his conversation always came back to the two interests nearest his heart — his former students and the philosophical implications of science, about which he loved to talk to a sympathetic listener, ever seeking the answer to the never to be answered question: what is the meaning of it all?

FRANK BLAIR HANSON

CHANCEY JUDAY

Chancey Juday (1871–1944) was so closely associated with Wisconsin and its lakes that we usually forget that his first twenty-nine years were spent in Indiana and that early in his career, after suffering an attack of tuberculosis, he also taught briefly at the Universities of Colorado and California, and was an investigator in the United States Bureau of Fisheries. Juday spent the academic year of 1907–08 in Western Europe where he made friends with the leading limnologists and visited lakes, biological stations, and universities. Two years later he studied four semi-tropical lakes in Central America.

In addition to his active work as biologist in the Wisconsin Geological and Natural History Survey, Dr. Juday became a Lecturer in the University of Wisconsin in 1908. Twenty-three years later, in 1931, he was made Professor of Limnology and after retirement in 1941, he devoted himself actively to his duties as Research Associate, a position he held at his death on March 29, 1944. At various times in his active career, he helped apply methods worked out in

Wisconsin to the study of lakes in other parts of the country including Alaska, Iowa, and New York. Juday's extended, productive scientific partnership with Edward A. Birge, long the grand old man of the University of Wisconsin, makes it difficult to think of one without including the other or to think of limnology without including them both.

Dr. Juday's first paper appeared in 1896 and dealt with the plankton of Turkey Lake, Indiana (Proc. Indiana Acad. Sci.). This work marked his entrance into the field of limnology which, after a slow start, was then undergoing rapid development. Along with various other phases of biology, limnology went into partial eclipse in the early years of the present century as a result of the burst of activity that followed the rediscovery of Mendelian heredity, with the accompanying emphasis on cytology, the expansion of experimental embryology, the continued preoccupation with evolution, and the promising beginning of currently popular fields like endocrinology. Even the meteoric interest in animal behavior and in eugenics helped turn attention from limnology as did the more aggressive growth of general ecology, of which limnology is an important part.

Throughout these early years of the current century, the years of Juday's thirties and forties, he continued to work in an overshadowed subject in the only way known to him, intelligently, inconspicuously and with quiet diligence; so quietly, in fact, that even workers in related fields learned of his personal worth — apart from his being the junior member of the famous limnological team of Birge and Juday — only slowly and belatedly.

Biology profited much from Professor Juday's efforts. This is especially true of those phases that he himself regarded as his field of special interest: "Biological significance of gases, dissolved in lakes; productivity of lakes; chemistry of lake waters; plankton; growth of fish in inland lakes." In all he was author or co-author of over a hundred publications, some of them extensive. The wide range and high value of his contributions to hydrobiology can be appreciated most easily by consulting the pages, or even the index of Welch's book on Limnology (1935). Juday's essay on the Heat Budget of Lakes (Ecology, 1940) is a minor masterpiece and illustrates well his ability to find and make use of quantitative data concerning a complicated subject. Professor Juday's final paper, although written in 1943, appeared posthumously and was characteristically a cooperative effort: Dutton, H. J. and Chancey Juday. Chromatic adaptation in relation to color and depth distribution of fresh water phytoplankton and large aquatic plants. Ecology, 25: 273-282, 1944.

Recognition came to Dr. Juday, though never to the full extent of his worth. His alma mater, Indiana University, conferred its LL.D. on him in 1933 and the Academy of Natural Sciences of Philadelphia chose him to receive its Leidy medal and award in 1943. His illness prevented the actual presentation until after his death.

Dr. Juday belonged to a generation that has furnished American zoology with an unusual number of outstanding men. I have known most of them well yet only Juday seemed to sense no age difference between us and only with Juday did I have to consult a reference book to find that he was, in fact, in an older generation. Others felt similarly toward him and many will miss his gentle, honest criticism and encouragement and his willingness to share his knowledge with any interested person. Like Thomas Henry Huxley, whom he scarcely resembled in any other way, he lived "to set a nobler tone to science . . ."

W. C. ALLEE

FRANK EUGENE LUTZ

Dr. Lutz was born at Bloomsburg, Pa. on September 15, 1879 and died November 27, 1943. Biologists in general and entomologists in particular will mourn his passing after an active period of some forty years during which he contributed much to our knowledge of insects. He received his college training at Haverford College, graduating in 1900. Later he studied at The University of Chicago, becoming a Master of Arts in 1902 and returning in 1907 to receive the degree of Ph.D. In the interim he studied for a time in the University College in London. From 1904 to 1909 Lutz was a member of the staff of the Carnegie Station for Experimental Evolution at Cold Spring Harbor. Having become interested in insects he was taken into the

Department of Invertebrate Zoology at the American Museum of Natural History, where he remained for the rest of his life as Curator of the Department of Entomology.

His zoological publications are numerous and touch on many fields of biology, although practically all deal primarily with insects. At Cold Spring Harbor he undertook some breeding experiments with the now famous fly, *Drosophila*, and it happened as a fortunate result of these that the attention of zoologists was called to the genetics of the pomace fly. Thus the great biological bonanza of the present century was uncovered. Although later concerned with other matters, Lutz always maintained a discerning interest in experimental zoology, and many of his contributions over the years fall into this category. Among such may be mentioned numerous studies on the reactions of insects to ultra-violet light and other physical factors in their environment. When dealing with such problems he was very astute and resourceful in devising appropriate apparatus, and further in viewing his own conclusions in the critical spirit so frequently reserved for the work of others.

As a natural result of his museum experience, he developed a considerable interest and expert knowledge in the taxonomy of insects and in the problems of geographical distribution. A number of his publications relate to this phase of entomology. These include especially studies on stingless bees and papers on the distribution of bees and other insects in the West Indian Islands. He was an ardent collector and amassed considerable material as the result of numerous personal excursions into the western United States and parts of the American tropics. These are now a part of the study collections of the American Museum which were also in other ways greatly enlarged during the long years that they remained in his charge.

His "Fieldbook of Insects" first published in 1918 went through several editions and has served to spread a knowledge of our common native insects among a large group of people, including many lay readers as well as college students. Very recently, another book dealing with the insect fauna of his own suburban back-yard appeared. This is written in more popular style, but includes numerous digressions to view the background of biology in very convincing fashion. Lutz exhibited a peculiarly invigorating style in his popular writings, and his public addresses to scientific gatherings were likewise enlivened by an unusual type of ready wit and humor. This detracted in no way from their more sober contents but may have given an occasional twinge to some of his more sedately conditioned colleagues.

Aside from his accomplishments in the rapidly expanding field of zoological research contemporaneous with his years of activity, Lutz's influence in education was felt through his curatorial work at the American Museum. This made itself manifest in numerous exhibits illustrating biological principles with insect material, and last but not least, in answering the innumerable queries that beset the conscientious museum curator. One educational innovation to which he gave a considerable amount of time was an out-door "insect zoo" or "nature walk" which included plants and other natural objects. This was undertaken in cooperation with the Interstate Park, near New York, and was kept in operation for some time through his efforts. The great variety of Dr. Lutz's biological interests must in some measure be attributed to his early associations as a student at Chicago. It was his good fortune that Whitman, Davenport, Williston, Lillie and Child were members of the zoological faculty there at that time.

With the passing of Dr. Lutz, American biology has lost an interesting and important figure: one whose activities were considerably at variance with those of the "teaching-research" schedule enjoyed by most of the other zoologists who contribute extensively to the advancement of their science.

CHARLES T. BRUES

RONALD FRASER MacLENNAN

Ronald Fraser MacLennan, member of the staff of the Department of Zoology at Oberlin College, died of coronary thrombosis on May 27th, 1944, about two weeks after the primary attack.

A graduate of Oberlin College in 1928, with honors in zoology, he received the Ph.D. degree at the University of California in 1932. At once appointed to an Instructorship at the State College

of Washington, he advanced to the Associate Professor rank in his eight years there, and was called back to his alma mater in 1940. In 1933 he married Marie Schulte, of Kansas City, Missouri, a graduate of Oberlin Conservatory of Music. He is survived by his wife and one son; by his mother and two sisters.

MacLennan's father, Simon Fraser MacLennan, was Professor of Philosophy at Oberlin; thus the son grew up in a scholarly atmosphere, as well as inheriting intellectual competency — maternally as well as paternally it should be said, in marked degree. Protozoology became the field of his research interest, in which he was inspired and counselled by Professor Charles A. Kofoid; and in the twelve years following completion of graduate study he published eighteen papers of distinct merit. He was also chosen to contribute the extended chapter on "Cytoplasmic Inclusions" in the composite work, "Protozoa in Biological Research" (1941), edited by Calkins and Summers.

While always fascinated by the search for new truth, it was in his skill as a teacher and in the richness of his personality that students, scientific associates, and fellow citizens of his community felt the resources of his character. Of chronically happy and sympathetic nature, he was easily approached and gave unstintedly of time and considered advice. A portion of a memorial tribute prepared by Professor R. S. McEwen, department head, and adopted by the Oberlin faculty reads:

All of us had every reason to assume that his would be a long and brilliant career. Of this there was abundant promise. It showed itself in his already numerous and significant publications, in the enthusiastic and affectionate relationships established alike with colleagues and students, and in many services for his church and for the village.

To those of us who were closest to him in his daily work, his ready and engaging smile, his unfailing wit and good humor, his quick assumption of his full share and more of any task however arduous, and his careful, critical yet unassuming scholarship were a constant inspiration.

MacLennan's membership in scientific organizations included the American Association for the Advancement of Science, American Microscopical Society, American Society of Zoologists, the Ohio Academy of Science, and the Corporation of the Marine Biological Laboratory at Woods Hole. At the time of his death he was Chairman of the Science Division of the college faculty, and President of the Oberlin Chapter of the American Association of University Professors.

Human nature being what it is, the permanent exit of a comrade and friend is a severe exaction; but when an intellect and spirit like that of Ronald MacLennan passes at the early age of thirty-eight, the ultimate loss to science and society is beyond computation. The American Society of Zoologists herewith recognizes this fact.

ROBERT A. BUDINGTON

WILLIAM EMERSON RITTER

Dr. Ritter (1856-1944) was variously known to zoologists as an expert upon the protochordate groups of tunicata and enteropneusta, as the author of extensive works upon biological philosophy, and as the first director of the Scripps Institution for Biological Research (the present Scripps Institution of Oceanography). To his younger associates he will be remembered as a sympathetic friend, with an exceptional gift of humor, as a man of wide learning, and an enthusiastic rider of various scientific hobbies.

Ritter's boyhood was spent upon a Wisconsin farm. He early engaged in public school teaching in his native state. His more advanced academic training came relatively late in life, his bachelor's degree at California (Berkeley) being attained in his thirty-second year, while his doctor's degree at Harvard came five years after that. Ritter's first published paper of which I find record dealt with "The parietal eye of some lizards from the western United

States'', and appeared in 1891 (Bull. Mus. Comp. Zool., Harvard). It was in this same year that he married Dr. Mary E. Bennett, who survives him. Ritter's academic positions were all in the University of California, ranging from that of Instructor in Biology to Chairman of the Department of Zoology, a position which he held until he assumed the Directorship of the Scripps Institution for Biological Research in 1909. Ten years after his retirement from the latter position in 1923, the degree of LL.D. was bestowed by the University upon Professor Ritter and upon Dr. Mary B. Ritter, his wife. Ritter's last honor, a posthumous one, was the naming of one of the Navy's "victory ships" after him.

Ritter's late entry into the scientific arena was more than compensated for by his exceptional productivity in his advanced years. His last book, bearing the characteristically whimsical title, "The California Woodpecker and I", was published in his eighty-second year, while he contributed a scholarly article (or at least it so seems to this writer) which appeared posthumously in *Philosophy of Science* (April, 1944). The title of this also deserves recording for a different reason: "Logic in our common knowledge or logic in the light of common sense, common knowledge, and common understanding."

Ritter's outstanding published work in the field of biological philosophy appeared in 1919 and bears the title "The Unity of the Organism, or the Organismal Conception of Life". It has as its "central idea" that "The organism in its totality is as essential to an explanation of its elements as its elements are to an explanation of the organism". The contrary viewpoint he characterizes as the "elementalist" one, and this viewpoint he seems to attribute, in varying measure to all other living biologists. For his central idea of the primacy of the "organism as a whole" Ritter can hardly claim originality, and indeed he quotes passages from Whitman, Wilson, F. R. Lillie and others which would seem to embody ideas scarcely distinguishable from his own. These men were relegated to the "elementalist" class, however, by virtue, it would seem, of their attempts to particularize this control of the whole over its parts.

Be that as it may, Ritter's insistence upon the importance of the whole organism, as such, in biology — i.e., his insistence that the organism creates its parts in development, rather than the parts creating the organism, and throughout life controls its parts, rather than the reverse — has probably had a salutary influence in biology. A salutary influence, that is, so far as it has had any influence at all. For it is doubtful whether "The Unity of the Organism" has had the influence which it deserved. One seldom sees it referred to, at least in biological publications.

While Ritter's writings were at times diffuse, or even somewhat lacking in coherence, occasional literary gems are to be found throughout them. Such an essay as that on "Feeling in the interpretation of nature" (*Scientific Monthly*, August, 1911) is worth reading, both as a self-revelation of Ritter, and as an example of wise counsel, well worded.

The Scripps Institution of Oceanography, at La Jolla, might fairly be regarded as Ritter's monument, though considerable of this credit must be shared with several of his colleagues at Berkeley, with his two energetic successors in the directorship at La Jolla, and of course with the Scripps family, whose liberal support made the Institution possible. But Ritter's untiring efforts, throughout a long term of years, were another essential factor in its creation.

Ritter was a large man with impressive features, certainly a man of distinguished appearance. Mentally, too, I think he must be credited with some of the elements of real greatness.

FRANCIS B. SUMNER

CHARLES PETER SIGERFOOS

Charles Peter Sigerfoos, Professor of Zoology Emeritus at the University of Minnesota, died at his home in Arcanum, Ohio, November 26th, at the age of 79. Dr. Sigerfoos was born May 4th, 1865. He received his B.S. degree from Ohio State University and his Ph.D. degree from The Johns Hopkins University and taught at Ohio State University, the University of Virginia, The Johns Hopkins University and finally the University of Minnesota where he served with great distinction during most of his active years.

Dr. Sigerfoos published few papers, but his research zeal never flagged, and he was always deeply engaged in the problems of fresh water invertebrates especially the Protozoa.

As a teacher, Dr. Sigerfoos had a long and singularly fruitful career, and his students and colleagues alike considered him one of the really great teachers of their generation. He had the rare gift of compelling students to their best effort and of leaving the impress of his subject and himself deeply and lastingly upon them. In part this was due to the close personal interest he had in the individual student. Even in the later years of his life he remembered in detail the many hundreds of students who had sat in his classes, and rarely indeed did he forget a name. As a result of this interest the students soon came to know him for what he was and he was chosen by them to serve in positions of the highest trust in their organizations for many years. At the time of his retirement his students, colleagues, and friends raised a substantial sum to establish the Charles Peter Sigerfoos Fellowship in Zoology, the income from which is used to assist graduate students at the University of Minnesota in studying at seaside and tropical laboratories.

Dr. Sigerfoos is gratefully remembered by the University of Minnesota as one of its greatest teachers, by his former students as an understanding and beloved counselor, and by his former colleagues as a staunch and devoted friend.

D. E. MINNICH.

COLIN CAMPBELL STEWART

Colin Campbell Stewart, Ph.D., Brown Professor of Physiology at Dartmouth College, died at Hanover, New Hampshire January 22, 1944, at the age of 70. Coming to Dartmouth from an Assistant Professorship at the University of Pennsylvania in 1904, he completed 39 years of teaching and research at the Dartmouth Medical School, of which he was Secretary and Acting Dean for 14 years. Meanwhile he taught physiology to academic students, and for 28 years was a Trustee of Mary Hitchcock Hospital.

Canadian by birth (Owen Sound, Ontario, August 15, 1873), A.B. degree Toronto 1894, Ph.D. degree Clark University 1897, he began teaching in 1898 at the Harvard Medical School, then at College of Physicians and Surgeons, Columbia, before going to the University of Pennsylvania in 1900.

His research dealt chiefly with muscle physiology (smooth, voluntary and cardiac), nerve supply to the cat's bladder, extra beat and compensatory pause, reactions to alcohol, and, finally, graphic analysis of the frog's heart action, upon which he made long-continued and still largely unpublished studies.

A stimulating, helpful and unselfish teacher, he was noted for quiet humor, skill at drawing and all sorts of constructive ingenuity — an expert in photography. In his prime, he was intermittently an out-door man, a mountain climber and always a keen student of flowering plants. He helped organize and develop the Dartmouth Outing Club. Later, he tended to become somewhat of a recluse devoted to research but always accessible, and companionable, to those seeking help and wisdom mixed with an abundance of Scotch wit and humor.

He married Zoe E. Smiley of Toronto in 1898. Their daughter, Dorothy Robson Stewart, Ph.D., is, like her father, a physiologist; their son, Colin Campbell, III, M.D., is Professor of Physical Diagnosis and Pediatrics in the Dartmouth Medical School.

J. H. GEROULD.

The foregoing resolutions were adopted by a rising vote and the Secretary was instructed to send copies to the nearest relatives and to publish the resolutions in the Proceedings of the Society.

3. *Report of the Treasurer.* The Treasurer presented the following report for the year 1944:

Credits:

Cash balance from 1943	\$1,139.61	
U. S. \$1,000 Savings Bonds M305107D and M305109D; present redemption value at \$850	1,700.00	
Receipts from dues	3,085.80	
Total		\$5,925.41

Expenditures:

Secretary's Expenses:

Stenographer and steno. supplies	202.50	
Printing, stationary, postage	261.25	
Telephone and telegraph	14.80	
Stipend	200.00	
		\$ 678.55

Treasurer's Expenses:

Stenographer and steno. supplies	40.00	
Postage	41.00	
		81.00

The Wistar Institute:

Programs and abstracts	585.72	
Proceedings	532.00	
		1,117.72

Biological Abstracts:

Subscriptions through Treasurer	8.00	
Contributions from members	1,452.00	
		1,460.00

Bank charge	1.16	
Members' checks returned	4.00	
Total expenditures	3,342.43	

Balance, December 30, 1944

Checking account	882.98	
Two U. S. Savings Bonds at \$850	1,700.00	
		2,582.98
Total		\$5,925.41
Total December 31, 1943		5,683.00
Increase of funds handled by Treasurer during current year		242.41
Decrease in assets of the Society during the current year		176.63

4. *Report of the Auditing Committee.* The Auditing Committee consisting of R. L. King and J. H. Bodine presented the following report:

Dr. H. W. Beams, Treasurer of the American Society of Zoologists for the year 1944, has handed us the books and accounts of the organization for audit. We find the records to be in good order and the books correctly balanced. The Treasurer's annual report is in accord with the books.

Signed: R. L. KING
J. H. BODINE

The report of the Treasurer, which could not be made available in time for approval at the September meeting, was submitted at the end of the year as usual. It was therefore necessary to submit this report, as well as that of the Auditing Committee, to the Executive Committee for approval.

The Executive Committee voted unanimously to accept and approve the reports of the Treasurer and of the Auditing Committee.

5. Report of the Executive Committee.

(a) Support of Biological Abstracts. The Committee recommended support of Biological Abstracts for 1945 on the same plan as for 1944, namely, that \$2.00 from each membership fee of \$4.00 be paid to Biological Abstracts.

It was voted to approve this recommendation.

(b) Appropriation for Union of American Biological Societies. The Committee recommended that \$15.00 be appropriated toward defraying expenses of the Union of American Biological Societies.

It was voted to approve this recommendation.

(c) Election of New Members. In accordance with the stipulations in the Constitution regarding membership, the Executive Committee recommended the following candidates for election to membership in the Society.

ACTIVE MEMBERS

(Formerly Associate Members)

Andrew, Warren	Grobman, Arnold Brams	Ryan, Francis Joseph
Ballentine, Robert	Moody, Paul Amos	Waggener, Roy Alfred
Eisenbrandt, Leslie Lee	Randall, Walter Clark	Zangerl, Rainer

(Not formerly Associate Members)

*Goodnight, Clarence James	*Mizelle, John Dary	Sperry, Roger Wolcott
Hard, Walter Leon	Morgan, Banner Bill	Taylor, Cecil A(lbert)
*Hoff, C(larence) Clayton	Schneirla, Theodore Christian	Wang, Hsi

NEW ASSOCIATE MEMBERS

*Baker, Clinton L(yle)	*Ferguson, Malcolm Stuart	Nickerson, Mark
Blane, Richard	Gabriel, Mordecai L.	Otis, Arthur Brooks
*Campbell, Robert Seymour	Granger, Barbara Samson	*Powers, Edward Lawrence, Jr.
Cooper, Ruth Snyder	*Humes, Arthur Grover	*Ryerson, Dwight Leonard
Daniel, George Edwin	Jones, Claiborne Stribling	*Tahmisian, Theodore Newton
Deane, Helen Wendler	Lyman, Rufus Ashley, Jr.	Wagner, Robert Philip
Eadie, William Robert	*Magalhaes, Hulda	Waugh, David Flyod
*Everett, Newton Bennie	*Meyer, Marvin Clinton	

It was voted that all candidates be elected as recommended by the Executive Committee, and the Secretary was instructed to cast one ballot in their favor.

* Names preceded by an asterisk are those whose applications were received during the autumn subsequent to the September meeting and prior to the November 15 deadline. The Executive Committee, in accordance with the powers granted by referendum, voted that these candidates be declared elected to the classes of membership indicated and instructed the Secretary to cast one ballot in their favor.

6. *Changes in membership.* For the information of the Society the Secretary reports the following changes in membership which have occurred during the past year. The following summary includes the above newly elected candidates:

Deaths	9	New associate members	23
Resignations	0	Reinstated	2
Dropped	0	New active members	9
	9		34
Total enrollment in last report		1,062	
Gain in enrollment		25	
Total enrollment at present		1,087	

7. *Election of officers.* The Nominating Committee consisting of Carl G. Hartman, Chairman; Charles Packard, and David H. Wenrich, presented the following report:

President, 1 year: A. S. Pearse.

Vice-President, 1 year: J. W. Gowen.

Treasurer, 3 years: A. C. Kinsey.

Executive Committeeman, 5 years: Sewall Wright.

Society Representatives on the Council of the American Association for the Advancement of Science, 1 year: A. Elizabeth Adams; Waldo L. Schmitt.

Society Representatives on the Council of the Union of American Biological Societies, 1 year: H. A. Charipper; T. L. Jahn.

Society Representatives on the Advisory Editorial Board of Biological Abstracts: R. K. Enders; E. J. Lund; A. Franklin Shull; H. J. Van Cleave.

Society Representative on the Executive Committee of the Biological Stain Commission: S. I. Kornhauser.

Members of the Editorial Board of the Journal of Morphology, 3 years: R. K. Burns; Mary J. Guthrie; A. S. Romer.

It was voted that the above named candidates for office be elected and the Secretary was instructed to cast one ballot in their favor.

8. *Committee Reports.* (a) The War Emergency Subcommittee of the Executive Committee consisting of C. G. Hartman, Chairman; M. H. Jacobs, J. S. Nicholas, L. L. Woodruff, T. S. Painter, and Sewall Wright and L. V. Domm, Ex officio, presented the following report:

The War Emergency Committee was practically inactive during the last year. It was felt that the Division of Biology and Agriculture of the National Research Council, under the direction of Chairman Robert F. Griggs and Dr. Ross G. Harrison, President of the Council, was functioning as effectively as any biological group could under the circumstances. Your chairman seconded the efforts of the Division whenever possible. Biology has not yet been "sold" to the Army and Navy; but the "military" is beginning to see the relation of biology to food production, protection, processing and preservation; of ecology to the prevention of disease; of physiology to aviation. Perhaps the twenty-five or more national biological societies will some day be organized (similar to the Institute of Physics) into an Institute of Biology, able to make an impress upon the legislative and executive departments, state and national, such that the men responsible for the civilization which is ours will seek the advice of experts in Biology as in Physics and Chemistry. In this war, of all the biological sciences, only Psychology was "ready", and it was the only one invited to participate in the war effort until the military came to realize that food and health are not produced by magic, any more than radar, plastics or explosives.

At the next meeting of the American Association for the Advancement of Science ought not Biology organize militantly?

(b) The following report by S. I. Kornhauser, Representative of the Society on the Executive Committee of the Biological Stain Commission, was presented:

As the societies' representative on the Biological Stain Commission, I wish to make the following report for the year 1944.

Early in the year the Executive Committee of the Commission for the Standardization of Biological Stains met in Philadelphia. At that time we received our charter from the State of New York as a non-profit corporation. The name was revised to the Biological Stain Commission. Several of us had felt that incorporation was necessary, inasmuch as the assets of the Commission had grown to over a hundred thousand dollars through the sale of large numbers of certification labels to the armed forces and Lend Lease. The income of this sum, we felt, if properly invested, would perpetuate the work of the Commission through years when the income from the sale of certification labels would not pay the annual expenses. Your representative was elected Treasurer of the corporation, and books were set up by a professional accountant. A finance committee was appointed to handle the investments, and I wish to report that the financial affairs of the corporation are on a very sound basis.

At the annual meeting the board of trustees was enlarged by the election of three members at large, two being professors at Columbia University and the third, the Dean of Cornell Medical School. We feel that their addition to the board of trustees will greatly strengthen the work of the Commission.

An important Committee on Research with Dr. William F. Windle, Vice-President of the Commission, as Chairman was established. Dr. Windle was given the task to find out what important lines of research on biological stains should be undertaken. It was felt that, in recent years so much weight had been put on routine testing and keeping our dyes up to standard, little progress had been made in advancing our knowledge of biological stains and their application. This committee on research will, we hope, inaugurate a new era of progress in the activities of the Commission.

Papers for Stain Technology fell off in quantity, due to the war, and the editor will gladly consider manuscripts dealing with microscopical methods. Here is a ready avenue of publica-

tion for papers of high quality. The fourth edition of *Biological Stains* is now exhausted and a fifth edition is being prepared.

(c) The Motion Picture Committee, consisting of Robert Chambers, Jr., Chairman; Ralph Buchsbaum, and O. W. Richards, working with E. J. Farris, representative of The Wistar Institute of Anatomy and Biology, submitted the following report:

The American Society of Zoologists Motion Picture Committee has been rather inactive during the past year, indirectly because of the war. A question has been raised regarding the publication of reviews of approved films in zoology, and it has been suggested that films of interest to zoologists particularly should have the reviews published in one of the zoological journals of The Wistar Institute.

It has been further suggested that the Committee request and invite films in zoology for viewing, in an effort to complete a list and make known the films that are available in zoology. At the last meeting considerable interest was shown by the members of the Society in attendance regarding films for teaching purposes. During the past year there were numerous inquiries received by The Wistar Institute regarding available films for teaching in zoology.

Plans are underway for an international organization made up of representatives of the leading scientific societies, to consider various motion picture problems.

The Committee recommends:

(a) That the American Society of Zoologists (Executive Committee) appoint annually a Committee to cooperate with The Wistar Institute in the Film Project.

(b) That the Society encourage its members to submit films to the Zoological Committee and The Wistar Institute for evaluation, and to contribute a copy of each approved film to the depository, in order to have at one location a complete file of films of zoological interest.

(c) That the Executive Committee appoint a representative of the Society to attend the forthcoming meeting of The American Committee on Biological and Medical Films, a national organization formed for the purpose of coordinating scientific and educational groups or individuals interested in planning, production, and use of biological and medical films.

It was voted that the foregoing committee reports be approved.

9. *Nominating Committee for 1945.* The President appointed the following nominating committee to prepare a slate of officers for the coming year: M. H. Jacobs, Chairman; A. E. Emerson, and J. S. Nicholas.

10. *Votes of Appreciation.* (a) A motion was made and unanimously passed expressing the thanks of the Society to the retiring Treasurer, H. W. Beams, for his loyal and efficient services to the Society during the past 3 years.

(b) It was voted to express the sincere thanks of the Society to the members of the local committee, consisting of J. Paul Visscher, Chairman; Ralph Bangham, Ralph W. Dexter, James C. Gray, Hope Hibbard, Thomas Surrarrer, and D'Alte Welch, and to Western Reserve University for the arrangements and cordial hospitality which served under difficult circumstances to make the Cleveland Meeting so successful.

The meeting was adjourned.

L. V. DOMM,
Secretary.

LIFE AND ACTIVE MEMBERS

(* indicates life members of the Society; † indicates charter members of the American Morphological Society; mail addresses are in italics.)

- ABRAMOWITZ, ALEXANDER ALBERT, B.A. (St. Stephen's), M.A., Ph.D., M.D. (Harvard), Research Assistant, *Biological Laboratories, Harvard University, Cambridge, Mass.*
- ACKERT, JAMES EDWARD, A.B., A.M., Ph.D. (Illinois), Professor and Head of the Department of Zoology, and Parasitologist, Agricultural Experiment Station; Dean, Graduate School; *Kansas State College, Manhattan, Kan.*
- ADAMS, A. ELIZABETH, B.A. (Mount Holyoke), M.A. (Columbia), Ph.D. (Yale), Professor of Zoology, *Mount Holyoke College, South Hadley, Mass.*
- ADAMS, LEVERETT ALLEN, A.B., A.M. (Kansas), Ph.D. (Columbia), Professor of Zoology, Curator of the Museum of Natural History, University of Illinois, *401 Vermont St., Urbana, Ill.*
- ADAMSTONE, FRANK BOLTON, B.A., M.A., Ph.D. (Toronto), Professor of Zoology, *345 Natural History Building, University of Illinois, Urbana, Ill.*
- ADELMANN, HOWARD BERNHARDT, A.B., A.M., Ph.D. (Cornell), Professor of Histology and Embryology, Chairman, *Department of Zoology, Cornell University, Ithaca, N. Y.*
- ADOLPH, EDWARD FREDERICK, A.B., Ph.D. (Harvard), Associate Professor of Physiology, School of Medicine, *University of Rochester, Rochester, N. Y.*
- AGERSBORG, H (ELMER) P (ARELI VON WOLD) K (JERSCHOW), B.S., M.S. (Washington), M.A. (Columbia), Ph.D. (Illinois), Professor of Biology, *Department of Biology, McKendree College, Lebanon, Ill.*
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Totals		
Life members		2
Active members		763
Associate members		322
Grand total		<u>1087</u>

ERRATUM

Abstract number 132, on page 45, *The Anatomical Record*, vol. 89, no. 4, Supplement, August 1944,

132. On the origin of the nervous system of vertebrates. F. H. Pike, Columbia University.

The second last sentence of the second paragraph should be omitted. It reads:

"This relationship is unknown or obscure in *Brachiopogitta* (Burfield)."

BOOK REVIEW

ATLAS OF THE BLOOD IN CHILDREN. By KENNETH D. BLACKFAN and LOUIS K. DIAMOND, with illustrations by C. Merrill Leister. With Foreword by George R. Minot. XIV and 1-158 pp., 70 colored plates and 19 charts in the text. New York: The Commonwealth Fund, 1944. Price \$12.00.

Books devoted exclusively to blood dyscrasias of infants and children are not numerous, and most of the larger texts and hand books of hematology do not give detailed descriptions of blood conditions in children. The "Atlas" will, therefore, prove to be a very important publication for pediatricians and others interested in various phases of hematology. Anatomists will be interested in the description and tabulation of blood values at different ages, from birth to the adult stage (pp. 6 to 10 and pl. 6), and in the anemia of prematurity (pp. 25 to 30) and its explanation.

The seventy plates printed in eight colors are the outstanding feature of the book. Most of them are from selected fields of blood films stained with Wright's stain, and opposite each plate is a key giving classification and description of the cells illustrated. The paintings done by Dr. Merrill Leister are faithful reproductions of what was seen, and the color printing is of the type we are accustomed to in the best European publications. A heavy subsidy by the Commonwealth Fund accounts for the excellent printing and relatively low selling price of the book.

"The illustrations are so classified as to facilitate identification of disease states. From the blood specimen under study, the predominating type of characteristic cell may be selected and through comparison with the plates presenting similar features a correct diagnosis of the disease can be made.

"The Atlas is based upon the study of the blood changes in more than 5,000 infants and children in the hematology laboratory of the infants' and childrens' hospitals in Boston since its establishment in 1927 by the late Dr. Blackfan and Dr. Diamond."

The text (144 pages and 13 pages of bibliography arranged according to diseases) is more extensive than would be expected in an atlas. It includes a brief chapter on hemopoiesis and normal blood values and blood pictures in infants and children. This is followed by descriptions of various blood dyscrasias with frequent reference to the plates. The disease entities are discussed under the headings of general considerations and etiology, symptoms, laboratory data, roentgenograms (for some conditions), diagnosis, course, prognosis, and treatment. One or two case records complete the description of each disease.

In the chapter on the blood cells the polyphyletic theory of hemopoiesis of Sabin, Doan and associates is followed without comment. This is unfortunate because it leads to wrong interpretation of some blood conditions and to mistakes in diagnosis in some instances. The theory assumes a separate parent cell for each type of blood cell: megaloblast for red cell, myeloblast for granulocyte, lymphoblast for lymphocyte, and a monoblast for the monocyte.

That the authors are confused by this theory is illustrated on plate 1, where the cells numbered 1 are called "megaloblasts." These are surely not the cells of pernicious anemia which Ehrlich named megaloblasts and which he distinguished sharply from the basophilic normoblasts shown here. The megaloblasts of Ehrlich do not occur in normal hemopoiesis and are not found in normal marrow or in the simple types of anemia. The anemias with megaloblastic marrow are of the pernicious anemia type and are due to failure of the anti-anemic liver factor, which may be due to various causes not necessarily leading to the development of a permanent Addisonian pernicious anemia, especially in children. It is surprising to note that the authors have not been impressed with the voluminous literature dealing with this subject which has been published in the last few years.

The term "lymphoblast" in the Sabin and Doan theory adds more confusion and misinterpretation of blood pictures. The left half of plate 4 illustrates the maturation of the lymphoid series. The source of the cells is not stated and one is lead to assume that they represent normal lymphopoiesis. Cells 1, 2 and 3 are labeled "lymphoblasts." These are evidently leukemic lymphocytes, for similar cells do not occur in normal human lymphatic organs and tissues. Interpretation of cells 5, 6 and 7 as young lymphocytes, as they are labeled here, might easily lead to a wrong diagnosis of leukemia.

The term "monoblast" adds more confusion as shown by the illustrations of these cells on plates 5, 59 and 60. The normal origin of monocytes is not known but it is generally agreed that in pathologic states they may be derived from the reticulum or from myeloblasts, and for this reason the monocytic leukemias have been classified as Schilling or Naegeli types, depending on the origin of the monocytes from the reticulum or from myeloblasts. The immature forms of these cells will vary in morphology according to their origin. It is, therefore, impossible to select one type of cell as the monoblast. Whether it is or not will depend on circumstances and the direction of differentiation.

The section on anemia is one of the most valuable and interesting sections of the book. It includes a classification of the various types encountered in infancy and childhood and splendid illustrations of blood pictures.

Chronic hypoplastic anemia is of special interest because so few cases of this type have been reported, and because there is no known cause for it. Survival of these children depends on repeated transfusions at regular intervals. The authors have studied five of these cases.

This anemia is defined as a "normocytic normochromic anemia which differs from aplastic anemia in that it involves chiefly a failure of red blood cell production without as much depression of the leukocyte or platelet elements." There is little effect on growth and development if transfusions are given at needed intervals. The anemia usually develops during the first three months of life. At eleven years, the oldest patient of the authors was fully developed and normal in every respect except for recurring anemia.

The anemia of prematurity is thought to be due to the same mechanism which induces the physiological anemia of the full term infant, probably the result of transition from oxygen unsaturation of the fetus in utero to the higher oxygen tension after birth. The premature infant grows faster than the full term infant, and a greater demand for blood is placed on a more immature hematopoietic

system. The severity of the anemia "is inversely proportional to the state of maturity, which may be roughly evaluated by the weight of the infant at birth."

Mediterranean anemia occurring in children of families of Mediterranean origin, and Erythroblastosis fetalis in which the Rh factor is usually involved are other types of anemia that should interest anatomists. Discussion of these is brief but adequate, and the eleven plates illustrating these two types of anemia are excellent.

The macrocytic hyperchromic anemias are discussed briefly and it is stated that "The existence of pernicious anemia in children has not been definitely proved by the presence of the criteria essential for the diagnosis of the disease in the adult, namely, absolute achlorhydria, recurrent glossitis, involvement of the spinal cord, and relapses after omission of liver treatment.

"However, pernicious-like anemia, implying a macrocytic anemia which may respond to liver extract principle, does occur in infancy and childhood and is due to a variety of causes other than permanent deficiency in the intrinsic substance of the stomach."

A number of etiological factors are listed, and it is stated that unless the anemia is due to some severe and permanent pathologic condition, it may be cured by a short course of liver treatment. The possibility of a megaloblastic marrow in some of these cases is not discussed, nor is anything said about the neutrophil leukocytes and their abnormal development in the marrow, which is so characteristic of pernicious anemia and some anemias of the pernicious type in adults. A study of these features in the marrow of children with this type of anemia would be very important.

Other types of anemia which are also seen in the adult are described and illustrated. This chapter includes sections on hemophilia and hemorrhagic diseases of newborn.

Chapter III deals with the leukocytes in disease, and includes normal leukocyte counts at different ages. The neutrophil leukocytosis present at birth is followed by a lymphocytosis of over 50% which persists throughout most of the first two years. The lymphocytosis of pertussis, infectious lymphocytosis and infectious mononucleosis is discussed and illustrated.

The different types of leukemia encountered are described in Chapter IV and illustrated on plates 52 to 68. The term "stem cell" leukemia is used for the cases in which it is impossible to classify the primitive leukemic cell as either lymphoid or myeloid. This would seem to indicate that the authors do have some sympathy for the neo-unitarian theory as opposed to the polyphyletic theory of hemopoiesis of Sabin. "Contrary to the opinion once prevalent, lymphoid leukemia is not much more frequent in the young than myeloid leukemia. It is possible that the exclusively immature "stem cells" were mistakenly identified as lymphocytes and that the misconception arose from this error."

Attention is called to the frequent difficulties of diagnosis of leukemia due to the hyperactive state of the hematopoietic system of the young in response to infectious and pathologic conditions.

Most of the plates showing blood pictures of leukemias are good, but some seem to have been made from badly faded blood films. This is seen in the nuclei of cells on plates 52 (right-hand portion of plate), 53, 67 and 68. The reviewer assumes that the peculiar nuclear pattern shown on these plates is due to fading,

because he has preparations which were perfect when first mounted but are now in the condition illustrated on these plates. A trace of acid in the mounting medium or on the slides or covers will cause this uneven fading in two or three years.

The behavior of the platelets in disease, primary thrombocytopenic purpura, thrombocytosis and thrombocythemia are discussed in Chapter V. This chapter is very brief but has decided practical value.

In conclusion it should be stated that this book is of very great practical value to all who are interested in the diagnosis and treatment of diseases affecting the blood of children and adults. Defects which will be noted by the hematologist are probably of little importance when the aim of the book is considered. Its arrangement, brevity, and above all, the plates make it a very valuable publication for consultation in the office, hospital or clinic.

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